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(54) Title: SOLID PHASE LIPOGLYCOPEPTIDE LIBRARY, COMPOSITIONS AND METHODS

(57) Abstract

The present invention relates to a library of distinct substances and compositions having the general formula R-P-S-L and P-S-L, representing solid support-bound lipoglycopeptides and free lipoglycopeptides, respectively. Combinatorial methods for the preparation of various libraries are described, as well as an assay for determining the biological activity of selected members thereof. In a specific embodiment, inhibitors of bacterial peptidoglycan synthesis are described.

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SOLID PHASE LIPOGLYCOPEPTIDE LIBRARY, COMPOSITIONS AND METHODS

1. Field Of The Invention

The present invention relates to the field of combinatorial library synthesis and drug discovery. In particular, the present invention relates to the synthesis of substances and compositions that mimic inhibitors of bacterial peptidoglycan synthesis. The substances and compositions of the invention are useful as potential drug candidates for the treatment of infectious disease, e.g., antibiotics.

2. Background Of The Invention

The biosynthesis of bacterial peptidoglycan is thought to proceed by a complex multi-step process. An early step in the biosynthetic process involves the synthesis of a lipid-linked disaccharide-peptido monomer unit. These monomer units are then linked together into a growing peptidoglycan chain by an enzyme exhibiting a transglycosylase activity. Subsequently, it is believed that the pendant pentapeptides of the peptidoglycan chain are crosslinked by the same or a separate enzyme exhibiting a transpeptidase activity. The transpeptidase reaction is inhibited by β-lactam antibiotics, such as penicillins or cephalosporins. See, e.g., Matsuhashi, M., in *Bacterial Cell Wall*, J.-M Ghuysen and R. Hakenbeck (Eds.), Elsevier Science B.V. (1994) pp. 55-71.

The structure of the naturally occurring lipid-linked glycopeptide intermediate is known. This intermediate consists of an N-acetylmuramic acid whose reducing end is linked to a pyrophosphoundecaprenyl group and to the D-lactyl group of which is attached a

pentapeptide, L-Ala-D-Glu-(A_2pm/Lys)-D-Ala-D-Ala. A_2pm stands for diaminopimelic acid. The intermediate may be represented by the formula UDP-MurNAc-pentapeptide. This intermediate is then transformed into the above-mentioned lipid-linked disaccharide-peptido monomer unit by a glycosyltransferase-mediated addition of an N-acetylglucosamine to the N-acetylmuramic acid. See, e.g., Van Heijenoort, J., in *Bacterial Cell Wall*, J.-M Ghuysen and R. Hakenbeck (Eds.), Elsevier Science B.V. (1994) pp. 39-54.

The synthesis of some compounds designed to inhibit bacterial call wall transglycosylation has been described. See, e.g., Hecker, S. J. et al., "Synthesis of Compounds Designed to Inhibit Bacterial Cell Wall Transglycosylation" *J. Org. Chem.* (1990) 55:4904-4911. No active compounds were ever described, however. Furthermore, the proposed compounds of Hecker et al. have not exhibited any remarkable activity.

The emergence of multiple drug resistant bacteria, in particular, vancomycin-resistant enterococci and methicillin resistant staphylococci, has prompted renewed searches for novel antiinfective agents. The majority of "cell wall" inhibitors in current use inhibit the latter stages of peptidoglycan biosynthesis, that is, transglycosylation or transpeptidation. Hence, most drug resistant bacteria have developed a resistance to these antibiotics.

The inhibition of the N-acetylglucosaminyl transferase that is encoded by the *murG* gene and which is involved in the biosynthesis of the lipid-linked disaccharide-peptido monomer unit is a promising candidate, thus. Bacterial *murG* has been cloned and its DNA sequence determined. Recombinant murG gene product is also known. It is further suspected that the N-terminal half of the gene product is responsible for binding of lipid intermediate. That portion of the

enzyme, which catalyzes the transferase activity, has yet to be determined, however.

Flavophospholipol is a known antibiotic produced by a group of grey-green Streptomyces, which disrupts the biosynthesis of peptidoglycans by inhibiting glycosyltransferase. It is used, mainly in cattle, as a performance enhancer, i.e., it improves the fattening capacity of cattle feed. Flavophospholipol exhibits a fairly broad spectrum of activity against gram-positive and gram-negative bacteria, but mostly against gram-positive microbes. However, both gram-positive and gram-negative organisms are known to carry extrachromosomally derived resistance to antibiotics. Indeed, the occurrence of bacteria in mammals, which are resistant to such antibiotics as penicillin, tetracycline, chloramphenicol and erythromycin, is quite high. Thus, the evolution of microbes bearing resistance to existing antibiotics, including flavophospholipol, is virtually assured.

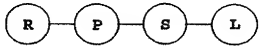
Consequently, the design and discovery of novel antiinfective agents, including antibiotics, is a constant, challenging and important endeavor. Techniques, which enhance the production and identification of drug or nutritional candidates, are always being sought. Such demands continue to evolve largely unfulfilled.

3. Summary Of The Invention

Accordingly, the present invention seeks to satisfy the need for new antiinfective agents, as well as the techniques for their synthesis and discovery, by providing a combinatorial approach to the preparation of a library of distinct substances having a predetermined general formula. In particular, the present invention provides a solid phase technique that allows for the synthesis of a large multitude of

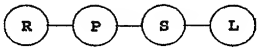
substances and compositions each representing a potential drug or nutritional candidate.

An important objective of the present invention is the production of a solid phase lipoglycopeptide library comprising a plurality of distinct substances of the formula

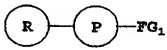


in which the group R comprises a solid support, the group P comprises one or more amino acids, peptides, or polypeptides, the group S comprises one or more sugars and the group L comprises one or more lipids.

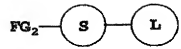
It is also an object of the invention to provide a method of preparing a solid phase lipoglycopeptide library having a plurality of distinct substances of the formula



comprising: (a) providing one or more groups R, P and FG_1 of the formula

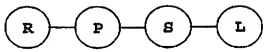


in which R comprises a solid support to which is bound the group P comprising one or more amino acids, peptides, or polypeptides, at least one member of the group P bearing the first functional group FG_1 capable of participating in a bond-forming reaction; (b) providing one or more groups S, L and FG_2 of the formula

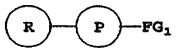


in which S comprises one or more sugars to at least one of which is bound a group L comprising one or more lipids, at least one sugar of the group S bearing the second functional group FG_2 capable of participating in the bond-forming reaction; (c) combining the one or more groups R, P and FG_1 and the one or more groups S, L and FG_2 such that the bond-forming reaction takes place to form a bond between that member of the group P, which bore the first functional group FG_1, to that sugar of the group S, which bore the second functional group FG_2.

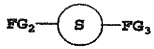
Alternative methods are also contemplated herewith. In a specific embodiment, a solid phase lipoglycopeptide library having a plurality of distinct substances of the formula



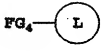
is prepared by the steps comprising: (a) providing one or more groups R, P and FG_1 of the formula



in which R comprises a solid support to which is bound the group P comprising one or more amino acids, peptides, or polypeptides, at least one member of the group P bearing the first functional group FG_1 capable of participating in an initial bond-forming reaction; (b) providing one or more groups S, FG_2 and FG_1 of the formula



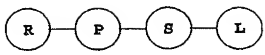
in which S comprises one or more sugars, at least one sugar of the group S bearing the second functional group FG_2 capable of participating in the initial bond-forming reaction and the same or another sugar of the group S bearing the third functional group FG_3 capable of participating in a subsequent bond-forming reaction; (c) combining the one or more groups R, P and FG_1 and the one or more groups S, FG_2 and FG_3 such that the initial bond-forming reaction takes place to form a bond between that member of the group P, which bore the first functional group FG_1, to that sugar of the group S, which bore the second functional group FG_2 to provide one or more initial bond-forming reaction products; (d) providing one or more groups L and FG_4 of the formula



in which the group L comprises one or more lipids, at least one lipid of the group L bearing the fourth functional group FG_4 capable of participating in the subsequent bond-forming reaction; (e) combining the one or more initial bond-forming reaction products and the one or more groups L and FG_4 such that the subsequent bond-forming reaction takes place to form a bond between that member of the group S, which bore the third functional group FG_3, to that lipid of the group L, which bore the fourth functional group FG_4.

Yet another objective of the present invention relates to selected compositions of the formula

which is obtained from a substance of the formula



by cleaving the group P from the group R, in which the group R comprises a solid support, the group P comprises one or more amino acids, peptides, or polypeptides, the group S comprises one or more sugars and the group L comprises one or more lipids. Moreover, synthetic compositions of the above-indicated formula, P-S-L, especially those prepared by combinatorial methods are also contemplated.

Other objects of the present invention will be apparent to those of ordinary skill in consideration of the disclosure provided herewith.

4. Brief Description Of The Drawings

Fig. 1 shows a diagram of the general combinatorial approach for the conjugation of sugar-containing units to solid support-bound peptides. Each unique combination, after cleavage from the solid support, is then placed in a particular well.

Fig. 2 illustrates the sequence of steps making up a parallel synthetic approach in which a sugar group S to which is bound a lipid group L is coupled to a solid support-bound peptide. Conjugation is followed by the removal of protecting groups and cleavage of the resulting lipoglycopeptide from the solid support. Alternatively, the groups S and L can be coupled to the solid support-bound peptide sequentially.

Fig. 3 shows the structures of preferred coupling agents that facilitate the condensation reaction involving functional groups of the members of P, S and L.

Fig. 4 provides an illustration of some of the sugar group disaccharide building blocks used in a particular library embodiment of the invention.

Fig. 5, Fig. 5a and Fig. 5b provides illustrations of some of the lipid and peptide building blocks favored in a particular embodiment of the invention.

Fig. 6 outlines the steps in the coupling, deprotection and cleavage of a particular R-P and S-L couple.

Fig. 7 is a schematic of a high throughput screening method designed to reveal active members of the library produced by the combinatorial approach of the present invention. Other assays can also be used, however. In particular, a probe can be constructed using the binding region of the active site of glycosyltransferase. The probe can then be used to screen and detect lipoglycopeptides having an affinity for the enzyme even while the potential ligands are still bound to the solid support.

Fig. 8 outlines the steps of a more preferred method of coupling a S-L group to a P-R group using one of the four coupling agents, e.g., EEDQ, HATU, HBTU, or PyBOP. The deprotection and cleavage steps are also shown.

5. Detailed Description Of The Preferred Embodiments

Consistent with the objectives of the invention, the present methods contemplate a combinatorial approach to the synthesis of a wide variety of potential antiinfective, nutritional and/or performance enhancing agents. In a specific embodiment of the invention, a parallel synthetic approach is illustrated. However, the present methods are applicable equally to other techniques, such as the "mix and split" approach. Indeed, after design and/or

selection of the desired constituents (i.e., the "building blocks") of the distinct substances, which are bound to the solid phase, an automated manner of combining the various ingredients can be readily appreciated in which a particular compartment of, for example, a planar solid surface can be assigned to a particular combination of molecular components.

On screening the unique library can present numerous opportunities to uncover a potent drug, performance enhancing, or nutritional component.

An important objective of the present invention is the production of a solid phase lipoglycopeptide library comprising a plurality of distinct substances of the formula, R-P-S-L, as defined earlier. In the library of the invention, more than one copy of each distinct substance may be present. Hence, multiple hits may be observed on screening of the library.

Suitable solid supports include most synthetic polymer resins, preferably in the form of sheets, beads, or resins, such as polystyrene, polyolefins, polymethyl methacrylates and the like, derivatives thereof and copolymers thereof. Polymers having varying degrees of crosslinking are also useful. A preferred solid support is a Merrifield resin, which is a 1% divinylbenzene copolymer of polystyrene. Generally, suitable polymer supports are insoluble in most organic solvents but swellable in some. Still other solid supports may be comprised of glass, ceramic, or metallic substances and their surfaces.

It is important, of course, that any solid support contain functional groups that can participate in condensation reactions, so that the molecular residues of choice may be bound or attached to the surface of the solid support. Such functional groups will generally involve halides, unsaturated groups,

carboxylic acids, hydroxyls, amines, esters, thiols, siloxy, aza, oxo and the like.

To facilitate coupling and later release of the solid phase synthesized lipoglycopeptide, linker groups may be used. Such linkers are well known in the art and may include, but are not limited to, polyamino, polycarboxylic, polyester, polyhalo, polyhydroxy, polyunsaturated groups, or combinations thereof.

The linker is preferably labile under a given set of conditions that do not adversely affect the compounds attached to the library or the reagents used in their preparation or manipulation. More preferably, the linker is acid labile or is photolabile. Desirable linkers include a halotrityl moiety (e.g., a chlorotrityl moiety) linking at least one member of the group P to the solid support or an alpha-halo (e.g., bromo) alpha-methylphenacyl moiety. Linkers, of course, may be used to covalently bind the various members of one group to each other or to members of other groups present in a given library.

Typically, covalent attachment may utilize functional groups comprising one or more amine, ether, thioether, ester, thioester, amide, acetamide, phosphate, phosphonate, phosphinate, or sulfate bonds. Because the library contains sugar moieties, the presence of one or more glycosidic bonds is expected, though not required. In a particular library of the invention at least one member of each group of the formula is covalently attached to at least one member of an adjacent group. Preferably, the same sugar of the group S is covalently attached to at least one member of the group P and to at least one member of the group L. Furthermore, the covalent bond attaching the lipid member of the group L to a sugar member of the group S may comprise a glycosidic ether bond, phosphate, pyrophosphate, phosphinyl, phosphanyl,

phosphonate, phosphonyl, phosphono, phosphino, phosphanoacetate, phosphonyl formate, phosphoramidyl phosphorothioate, phosphonylsulfonate, phonphonylsulfonate bond, or the like. Examples of some glycosidic bonds are shown on Figure 5b. Still, it may also be desirable to have at least one sugar of the group S to be covalently attached to a lipid of the group L through an anomeric alpha-hydroxy acetamide bond. More particularly, at least one sugar of the group S is covalently attached to a member of the group P through a C-3 hydroxy alpha-acetamido or alpha-propionamido moiety.

Any combination of amino acid residues can be used in the present library and its method of preparation. In certain situations the amino acid, peptide, or polypeptide of the group P may be comprised exclusively or predominantly of hydrophilic amino acid residues, however. It is also possible that the members of the group P comprise exclusively or predominantly of hydrophobic amino acid residues. Various combinations of amino acids, peptides and polypeptides, including both stereoisomers, analogs, or homologs thereof are provided in Fig. 5.

The group S may comprise one or more monosaccharides, disaccharides, or polysaccharides, as illustrated in the exemplary sugar group of Fig. 4. In particular, a monosaccharide of the invention may be a hexose, pentose, deoxy analog thereof, dideoxy analog thereof, azido-substituted analog thereof, or amino-substituted analog thereof. Also, a disaccharide or polysaccharide of the invention may include hexoses, pentoses, deoxy analogs thereof, dideoxy analogs thereof, azido-substituted analogs thereof, amino-substituted analogs thereof, or combinations thereof.

The various potential covalent linkages among sugars are permissible under the present invention.

Thus, alpha or beta stereochemical configurations may be present, as are cis-1,2 or trans-1,2 arrangements. The bonds between the sugars may be (1,6), (1,3), (1,4) and the like, including the possible stereochemical configurations.

A whole host of different lipids may be used in the present invention. Such lipids may be simple or quite complex. The lipid may be saturated, unsaturated, or polyunsaturated. It may be linear, branched or cyclic. It may be made up exclusively or partially of aliphatic group comprising 2-60 carbon atoms, preferably 5-55, more preferably 10-40, most preferably 15-30. Simple fatty acid chains may be useful, as are cholesterol-inspired structures. Further, the lipids may be branched or unbranched alkyl or alkenyl (optionally substituted by one or more lower alkoxy, lower acyloxy, halogen, or aryl); branched or unbranched acyl (optionally substituted by one or more lower alkoxy, lower acyloxy, halogen, or aryl); lower alkoxycarbonyl, optionally substituted by one or more lower alkenyl, lower alkoxy, lower acyloxy, halogen, aryl, or 9-fluorenyl; or
silicon, substituted by one or more lower alkyl, lower alkoxy, or aryl. Moreover, simple or complex aromatic or heteroaromatic structures may also be useful. Examples of aromatic structures include, but are not limited to, aromatic carboxylic acids such as, subsituted or unsubtituted hydroxyphenylacetic acid, hydroxyphenylproprionic acid, methylbenzylate, hydroxynaphthoic acid, hydroxy-biphenylcoaboxylic acid, hydroxy-fluorenecarboxylic acid, hydroxybenzamide; heteroaromatic structures such as, substituted or unsubstituted hydroxybenzofuran, hydroxyquinoline, thiophencarboxylic acid, hydroxythianaphthenecarboxylic acid and the like. Examples of some aromatic lipids are shown in Figure 5a.

An important aspect of the invention is the method by which the solid phase lipoglycopeptide library is prepared. The method includes providing one or more groups R, P and FG_1 of the formula, R-P-FG_1, as defined above. This material is allowed to react with a second unit having the formula, FG_2-S-L, also as defined above, such that the bond-forming reaction takes place to form a bond between that member of the group P, which bore the first functional group FG_1, to that sugar of the group S, which bore the second functional group FG_2.

In specific embodiments of the invention, as described in greater detail in the Examples Section of the disclosure, the resin is first soaked with an organic solvent that swells the resin prior to the combination step. If the functional group FG_1 of the resin-bound component is protected, it is understood that the protecting group, such as fluorenylmethyloxycarbonyl (Fmoc), must first be removed. Thus, the method may entail the removal of any protecting groups present on groups P, S, or L.

The combination step in which the respective functional groups are allowed to react will preferably be facilitated by the addition of activating or coupling agents, which are well known to those of ordinary skill. Such agents assist in the formation of a bond between, e.g., a carboxylic acid and an amine group.

After the desired condensation reactions have been carried out, the resulting solid support-bound library of lipoglycopeptides can then be released from the solid support or screened while still solid support bound. Thus, it is specifically contemplated that the resulting lipoglycopeptide library be screened for one or more active substances using one or more probes, receptors, affinity binders, enzymes or whole cells.

If the compounds are to be released from the solid support, the group P is cleaved from the group R to provide the structural unit P-S-L, which is then recovered.

In one of the methods described above, one or more groups S, L and FG_2 are combined with the one or more groups R, P and FG_1 at room temperature in a solvent in the presence of an activating agent. The functional group FG_2 may comprise a pentafluorophenyl ester or simply a free carboxylic acid, especially when allowed to react with an amino group in the presence of an activating agent, such as EEDQ, HATU, HBTU, PyBOP, or the like. The various functional groups may be located anywhere in the molecular unit, including the ends or on the side chain, especially of a member of the group P.

While some naturally occurring entities of the general formula P-S-L are known, the present invention also contemplates novel combinations of the different elements of the general formula. And even with those known compounds, those that are prepared by a solid phase method or by the cleavage of the bond between the groups R and P, as defined herein, are considered to be a part of the invention. Hence, specific synthetic versions of compounds of the general formula are contemplated. A combinatorial approach to synthesis is the preferred route.

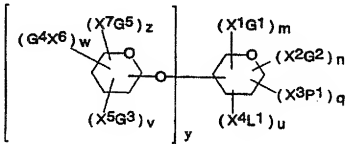
Of note, certain compounds of the general formula may differ from natural counterparts in the number of amino acid residues present in the group P. Preferred compounds comprises two or more amino acids in sequence, more preferably, four or more, most preferably six or more. The group P may further comprise one or more peptides or polypeptides, which may be joined in sequence or separated by non-peptide moieties, including linker groups.

Still other polypeptide components may possess three or more amino acids in sequence or two or more sugars, preferably three or more sugars.

As stated elsewhere, the lipid portion of the compounds of the instant library can vary widely in structure. Typically, however, the lipid group will comprise 4-60 carbon atoms, preferably 5-50 and more preferably 10-30.

Further, the various structural units, which can be prepared by the present methods, may or may not correspond with the structure of a naturally occurring lipid linked glycopeptide intermediate. In certain cases, it may be of benefit that the group L, if comprising a single lipid, does not include an undecaprenyl group.

Thus, the present invention contemplates compounds of the general formula (I):



(I)

in which

L^1 comprises a lipid group;

P^1 comprises one or more amino acids, peptides or polypeptides;

G^1, G^2, G^3, G^4, or G^5 can each independently be a substituted or unsubstituted, branched or unbranched alkyl, alkoxy, alkenyl, C1-C8 acyl, acetyl,

alkoxycarbonyl, hydroxyalkyl, carboxyalkyl group or a substituted or unsubstituted aromatic or heteroaromatic group, or hydrogen;

X^1, X^2, X^5, X^6 or X^7 can each independently be a functional group comprising an oxyalkyl, amine, ether, thioether, ester, thioester, amide, acyl, acetamido, phosphate, phosphinate, pyrophosphate, sulfate, azido, hydroxy group or hydrogen, provided that if the functional group is azido, hydroxy, or hydrogen the attached G group is not present;

X^3 or X^4 can each independently be a functional group comprising an amine, ether, thioether, ester, thioester, amide, acetamide, phosphate, phosphinate, pyrophosphate, sulfate group;

y is 0, 1, 2, or 3;

m, n, v, w, or z can independently be 0, 1, 2, or 3;

q or u can independently be 1, 2, or 3 provided that the sum of q and u is not greater than 5, provided that such compounds do not include: 2-N-Acetyl-1-α-*O*-allyl-4,6-*O*-isopropylidenemuramyl-L-alanyl-D-glutamine benzylester; (2R)-Benzyl 2-[N-(2'-N-Acetyl-1'-α-*O*-allyl-4',6'-*O*-acetylmuramyl-L-alanyl)amino]-4-cyanobutanoate; (2R) Benzyl 2-N-Acetyl-1'-α-*O*-allyl-4,6-*O*-isopropylidenemuramyl-L-alanyl)amino]-4-cyanobutanoate; (2R,2''R)-Benzyl 2-[N-[2'-N-Acetyl-1'-α-*O*-[(N,N-diisopropylamino)(butoxy)phosphinyl]-4',6'-di-*O*-acetylmuramyl-L-alanyl]amino]-4-cyanobutanoate; (2R,2''R)-Benzyl 2-[N-[2'-N-Acetyl-1'-α-*O*-[[2''-carbobenzoxy-2''-(pentyloxy)ethoxy](benzyloxy)phosphoryl]-4',6'-di-*O*-acetylmuramyl-L-alanyl]amino]-4-cyanobutanoate; (2R,2''R)-2-[N-[2'-N-Acetyl-1'-α-*O*-[[2''-carboxy-2''-(pentyloxy)ethoxy]hydroxyphosphoryl]muramyl-L-alanyl]-amino]-4-cyanobutanoate; or the natural substrate for either the transglycosylase activity of penicillin

binding proteins or the N-acetylglucosaminyl transferase activity of the murG gene product.

In particular, the compound of formula (I) comprises lipoglycopeptides in which groups X^1G^1, X^5G^2, X^6G^5, or X^7G^4 can be a hydroxyl, $HOCH_2CH_2$-, acetamide, phthalimido, benzoyl, alkoxybenzoyl, alkoxycarbonylalkyl, carboxyalkyl, pivaloyl group or any substituents commonly found on carbohydrates. The X^1G^1 or X^2G^2 groups are preferably located on position 2 or 5 of the ring, group X^2P^1 preferably located on position 3, and group X^4L^1 preferably located on position 1 of the ring. The compound of formula (I) further comprises one or more peptides or polypeptides, and one or more lipids. Perferably each peptide or polypeptide comprises three or more amino acids in sequence and each lipid comprises one or more saturated, unsaturated, or polyunsaturated linear, branched or cyclic aliphatic group comprising 2-60 carbon atoms, or one or more substituted or unsubstituted aromatic or heteroaromatic groups. The lipid and sugar can be linked via covalent attachment of X^4 including a glycosidic ether bond, phosphate, pyrophosphate, phosphinyl, phosphanyl, phosphonate, phosphonyl, phosphono, phosphino, phosphanoacetate, phosphonyl formate, phosphoramidyl phosphorothioate, phosphonylsulfonate, or phonphonylsulfonate bond.

The present invention is further illustrated by the following specific examples. These examples should not be construed as limiting the invention in any way, as they are not required to practice the invention, which has already been described adequately above.

6. Examples - Preparation Of Sugar, Lipid and Sugar-Lipid Building Blocks

6.1. Allyl 2-Acetamido-2-deoxy-D-glucopyranoside (2)

A suspension of acetamido-2-deoxy-D-glucose (1) (22.1 g, 0.1 mole) in dry allyl alcohol (400 mL) containing boron-trifluoride etherate (2 mL) is heated under reflux for 2 h. The clear solution is cooled, kept overnight at room temp, and evaporated to afford the title compound (α:β ratio 4:1), as a crystalline mass. TLC (ethyl acetate, isopropyl alcohol, water 9:4:2) Rf 0.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.64 (d, 1H), 5.78-5.95 (m, 1H), 4.98-5.31 (m, 2H), 4.65 (d, 0.8H, J = 2.4Hz, H-1α), 4.27 (d, 0.2H, J=8.4Hz, H-1β), 3.11-4.22 (m, 11H), 1.83 (s, 3H).

6.2.
Allyl 2-acetamido-4,6-O-benzylidine-2-deoxy-α-D-glucopyranoside (3)

Compound (2) (5 g, 0.019 mole) is dissolved in DMF (30 mL). Benzaldehyde dimethyl acetate (5.7 mL, 0.038 mole) and p-toluenesulfonic acid (380 mg, 0.002 mole) are added. The reaction is kept at 70 °C overnight for 18 h. The reaction mixture is worked up by the addition of water, followed by sodium bicarbonate to neutralize the resulting mixture and precipitate the product. The precipitated product is filtered and washed well with water. Recrystallization from methanol/water provides pure α isomer (3.2 g, 47%). TLC (10% methanol/methylene chloride) Rf 0.7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.52 (m, 5H), 5.84-5.92 (m, 2H), 5.57 (s, 1H), 5.24-5.34 (m, 2H), 4.89 (d, 1H, J = 3.3Hz), 3.00-4.30 (m, 9H), 2.06 (s, 3H).

6.3.
Allyl 2-Acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-2-deoxy-3-O[1-(R)-(methoxycarbonyl)ethyl]-α-D-glucopyranoside (8)

Compound (6) (150 mg, 0.43 mmole) and compound (7) (214 mg,0.65 mmole) are dried by azeotropic distillation from toluene 2 times, finally dissolved in toluene (10 mL). To this mixture is added p-

toluenesulfonic acid (10 mg). It is heated at 110 °C for 3 h. The solvent is concentrated under reduced pressure, and the mixture is passed through a silica gel column. Elution with methylene chloride, then with increased percentage of methanol in methylene chloride up to 5% methanol in methylene chloride, gives the product (200 mg, 70%). TLC (10% methanol/methylene chloride) Rf 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, J = 4.2Hz), 5.83-5.91 (m, 2H) 5.00-5.34 (m, 8H), 4.77 (d, 1H, J = 3.6Hz), 3.78-4.27 (m, 8H), 3.75 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.43 (d, 3H, J = 6.9Hz). MS FAB: 700 (M+Na)$^+$.

6.4.
Allyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O[1(R)-(methoxycarbonyl)ethyl]-α-D-glucopyranoside (9)

Compound (8) (200 mg, 0.3 mmol) is dissolved in pyridine (2 mL). To this solution is added acetic anhydride (1 mL) and DMAP (10 mg). The reaction is stirred at room temperature for 6 h, and it is evaporated under reduced pressure. The residue is taken up into water (10 mL) and extracted twice with ethyl acetate. The organic extract is washed with water and saturated sodium chloride solution, then dried over sodium sulfate and filtered. After evaporating the solvent, crystalline product (210 mg 100%) is obtained. TLC (10% methanol/methylene chloride) Rf 0.62. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H), 5.80-5.84 (m,2H) 5.03-5.31 (m, 6H), 4.45 (d, 1H, J = 8.4Hz), 3.80-4.25 (m, 12H), 3.78 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.93 (s, 3H), 1.35 (d, 3H, J = 7.2Hz). MS FAB: 742 (M+Na)$^+$.

6.5.
Carboxymethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-

glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[1(R)-(methoxycarbonyl)ethyl]-α-D-glucopyranoside (10)

Compound (9) (200 mg, 0.28 mmol) is dissolved in a mixture of solvents: carbon tetrachloride (0.8 mL), acetonitrile (0.8 mL) and water (1.2 mL). This mixture is treated with sodium periodate (250 mg, 1.17 mol) and ruthenium(III) chloride (2 mg). The reaction mixture is stirred at room temperature for 2 h. Precipitation of $NaIO_3$ is observed. The mixture is extracted with CH_2Cl_2 (2 x 15 mL). The organic layer is washed once with water and dried over Na_2SO_4. After filtration, the solvent is evaporated to give the product (180 mg, 86%) as a solid. Rf 0.1. ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 1H),6.40 (m, 1H), 5.07-5.35 (m,6H), 4.45 (d,1H, J = 8.4Hz), 3.83-4.28 (m, 12H), 3.79 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H),2.02 (s, 3H), 1.98 (s, 3H), 1.36(d, 3H J = 7.2Hz). MS FAB: 759 (M+Na), 782 (M+2Na)$^+$.

6.6.
Dodecylcarbamoylmethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[1(R)-(methoxycarbonyl)ethyl]-α-D-glucopyranoside (11)

Compound (10) (700 mg, 0.95 mmol), 1-hydroxybenzotriazole (142 mg, 1.05 mmol), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (445 mg, 1.05 mmol) (WSCDI), and dodecylamine (210 mg, 1.14 mmol) are stirred in methylene chloride (40 mL) for 30 h. The reaction mixture is diluted with methylene chloride (60 mL), washed with water, saturated NaCl solution, then dried with sodium sulfate. The organic layer is filtered, and the solvent is removed under vacuum. The residue is purified by chromatography on silica using a solvent elution gradient of CH_2Cl_2-7% EtOH/CH_2Cl_2 to give the product (620 mg, 73%) as a crystalline solid. TLC (10% methanol/methylene chloride) Rf 0.6. ^1H NMR (300 MHz,

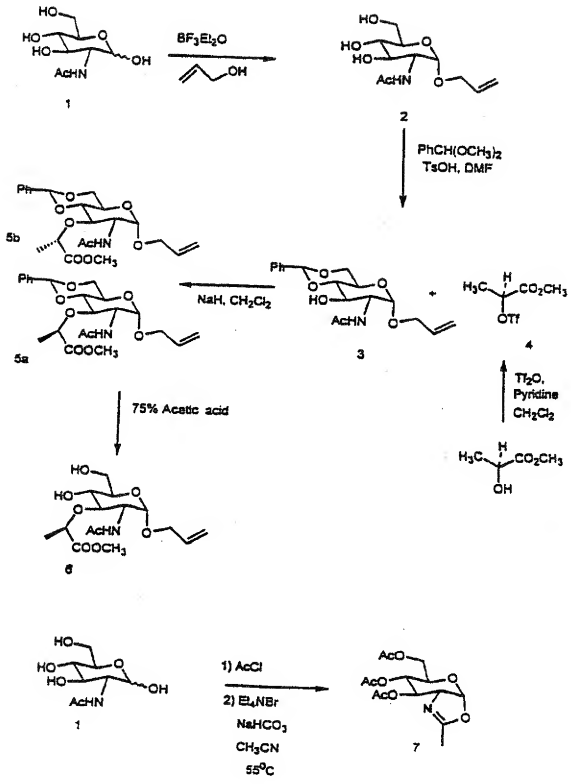
$CDCl_3$) δ 8.21 (s, 1H), 6.80 (m, 1H), 6.37 (d, 1H, J = 8.4Hz), 5.50 (s, 1H) 4.95-5.28 (m, 3H), 4.65 (d,1H J=8.1Hz), 3.21-4.29 (m, 12H), 3.78 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H) 1.53 (m, 2H), 1.36 (d, 3H, J = 6.9Hz), 1.25 (m, 20H), 0.87 (t, 3H J=7.2Hz). MS FAB: 926 $(M+Na)^+$.

6.7.
Dodecylcarbamoylmethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[1(R)-(carboxy)ethyl]-α-D-glucopyranoside (12)

Compound (11) (100 mg, 0.11 mmol) is dissolved in 1,4-dioxane (10 mL) and stirred at ice bath temperature. An 0.1M aqueous solution of potassium hydroxide (1.7 mL, 0.17 mmol) is added to the mixture, and it is stirred for 4 h at 0 °C. The reaction mixture is worked up by neutralizing with amberlite H^+ resin. The reaction mixture is filtered and the solvent evaporated to give the product (90 mg, 91%) as a solid. TLC (20% methanol/methylene chloride) Rf 0.45. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H),6.80 (d, 1H), 6.40 (d, 1H) 5.50 (s, 1H), 3.21-5.08 (m, 17H), 2.01-2.08 (m, 18H), 1.94 (d, 3H, J = 6.3Hz), 1.25 (m, 20H), 0.87 (t, 3H, J = 6.9Hz). MS FAB: 912 $(M+Na)^+$, 935 $(M+2Na)^+$.

6.8.
Dodecylcarbamoylmethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[1(R)-(pentafluorophenoxycarbonyl)ethyl] α-D-glucopyranoside (13)

Compound (12) (50 mg, 0.056 mmol) is dissolved in methylene chloride (10 mL). To this solution is added pentafluorophenol (12 mg, 0.067 mmol) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (29 mg, 0.067 mmol). This mixture is stirred for 2 days at room temperature. The reaction mixture is diluted with methylene chloride and washed well with ice-cold water, and ice-cold saturated NaCl solution, then dried over sodium sulfate. This mixture is filtered and the solvent evaporated to dryness to give the product (53 mg , 89%) as a solid. TLC (Ethyl acetate:acetone 4:1) Rf 0.7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23(s, 1H), 7.05 (m, 1H), 6.21 (d, 1H), 5.43(s, 1H) 23.25-5.19 (m,15H), 1.95-2.17 (m, 15H), 1.58 (d, 3H, J = 6.9Hz), 1.24 (m, 20H), 0.87 (t, 3H, J=6.9Hz).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5b
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OTf
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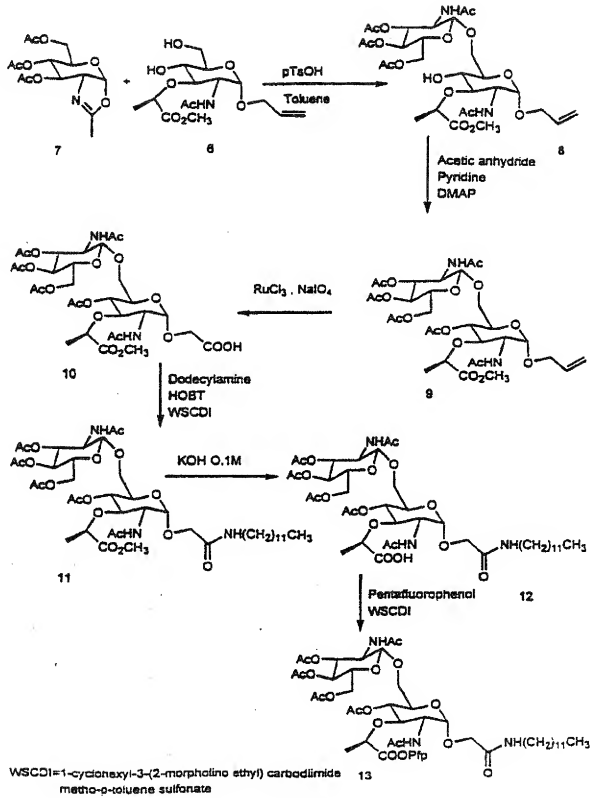

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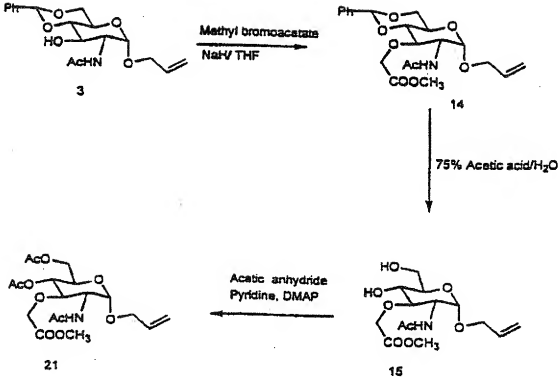
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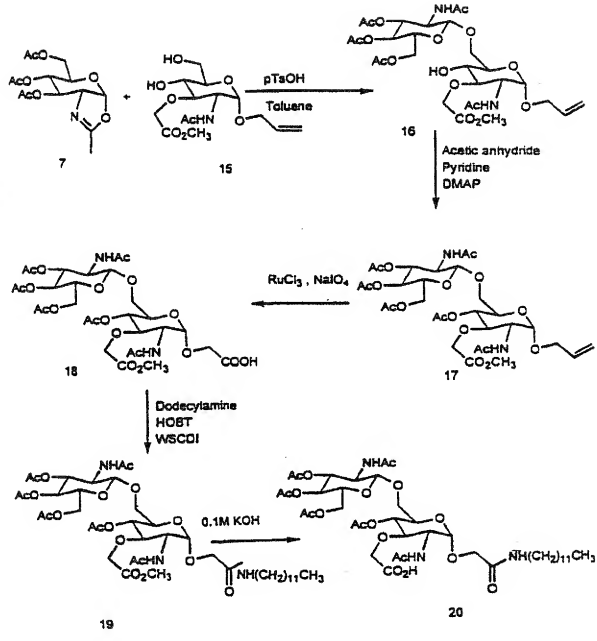
HO
HO
AcHN
COOCH3
15



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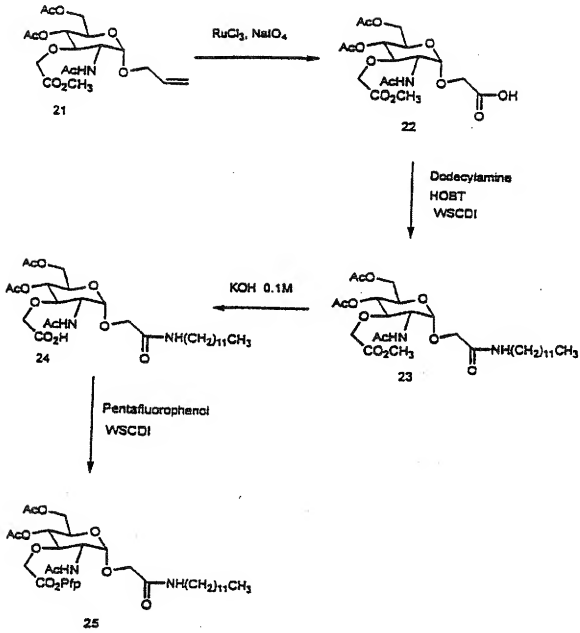
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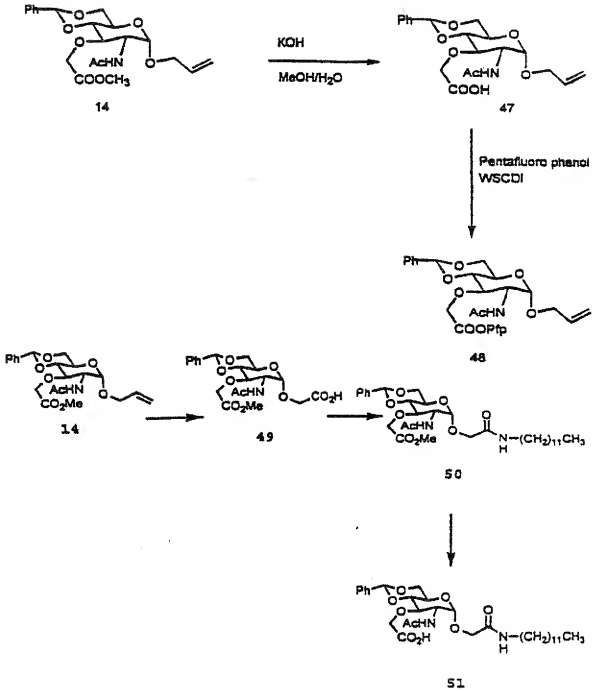
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Ph
AcHN
CO2Me
14
Ph
AcHN
CO2Me
CO2H
49
Ph
AcHN
CO2Me
O
N—(CH2)11CH3
H
50
Ph
AcHN
CO2H
O
N—(CH2)11CH3
H
51

6.9.
Allyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (14)

Compound (3) (349 mg, 1 mmol) is dissolved in THF (10 mL), and to this solution is added 60% NaH in oil (80 mg, 2 mmol). The above mixture is stirred at room temperture for 30 min under argon. To this mixture is added methyl bromoacetate (0.19 mL, 2 mmol). The above mixture is stirred at 50 °C for 23 hr under argon. Acetic acid (2 mmol) is added to quench the reaction. The solvent is evaporated and water (10 mL) is added to the residue. After stirring, the precipitated product is filtered and dried (420 mg, 100%). TLC (10% methanol/ methylene chloride) Rf 0.55. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.48 (m, 5H), 5.83 (m, 1H), 5.56 (s, 1H), 5.17-5.31 (m, 3H), 3.76-4.50(m, 10H), 3.73(s, 3H), 2.05 (s, 3H). MS FAB: 444 (M+Na)$^+$.

6.10a.
Allyl 2-acetamido-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (15)

Compound (14) (1.5 g, 3.6 mmol) is treated with 75% acetic acid /water and further processed as described for compound (6) to give the product (810 mg, 67%) as a solid. TLC (10% methanol/ methylene chloride) Rf 0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (d, 1H), 5.80-5.9 (m, 1H),5.20-5.31 (m, 2H), 5.19 (d, 1H, J= 3.6 Hz), 4.52 (ABq, 2H) 3.44-4.24 (m, 10H), 3.77 (s, 3H), 2.09 (s, 3H). MS FAB: 356 (M+Na)$^+$.

6.10b.
Allyl 2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-[methoxycarbonyl methyl]-α-D-glucopyranoside (21)

Compound (15) (750 mg, 2.25 mmol) is treated with acetic anhydride and pyridine with catalytic amounts of DMAP overnight, as in example (9), to give the product

(21) (500 mg, 53%) as a solid. TLC (ethyl acetate: acetone 4:1) Rf 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.05-5.31 (m, 3H), 3.82-4.39 (m, 10H), 3.77(s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H). MS FAB: 440 (M+Na)$^+$.

6.11.
Allyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-2-deoxy-3-O[methoxycarbonylmethyl]-α-D-glucopyranoside (16)

Compound (15) (2.2 g, 6.6 mmol) and compound (7) (3.5 g, 10.6 mmol) are heated with p-toluenesulfonic acid (150 mg) in toluene (150 mL) in a similar manner as in compound (8) to give compound (16) (3.0 g, 68%). TLC (10% methanol/methylene chloride) Rf 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (m, 1H), 5.82-5.94 (m, 2H) 4.59-5.31 (m, 7H), 3.77-4.29 (m, 14H), 3.75 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 2.02 (2s, 6H), 1.96 (s, 3H). MS FAB: 685 (M+Na)$^+$.

6.12.
Allyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O[methoxycarbonyl methyl]-α-D-glucopyranoside (17)

Compound (16) (3.0 g, 4.5 mmol) is treated with pyridine (30 mL), acetic anhydride (15 mL), and DMAP (30 mg) in the same manner as for compound (9). After recrystallization from ethyl acetate, pure compound (17) (1.1 g, 36%) is obtained. TLC (ethyl acetate) Rf 0.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1H), 5.85 (m, 1H), 5.02-5.31 (m, 5H),4.45 (d, 1H), 3.80-4.32 (m, 11H), 3.75 (s, 3H), 3.35 (dd, 1H),2.14 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (m, 6H), 2.00 (s, 3H), 1.93 (s, 3H). MS FAB: 727 (M+Na)$^+$.

6.13.
Carboxymethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (18)

Compound (17) (420 mg, 0.6 mmol) is treated with sodium periodate (510 mg, 2.4 mmole) and ruthenium(III) chloride as in compound (10) to give compound (18) (333 mg, 77%) as a solid. TLC (10% methanol/ methylene chloride) Rf 0.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H), 6.60 (m, 1H), 4.82-5.16 (m, 5H), 3.49-4.51 (m, 13H), 3.76 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (m, 6H), 2.00 (s, 3H), 1.96 (s, 3H). MS FAB: 745(M+Na)$^+$, 767 (M+2Na-H)$^+$.

6.14.
Dodecylcarbamoylmethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (19)

Compound (18) (330 mg, 0.46 mmol) is treated with 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-

toluenesulfonate (292 mg, 0.69 mmol) and dodecylamine (102 mg, 0.55 mmol) in a similar manner to compound (11). After silica gel column purification compound (19) is obtained (250 mg, 61%) as a solid. TLC (10% methanol/methylene chloride) Rf 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H), 6.86 (m, 1H),6.34 (m, 1H), 4.95-5.35 (m, 5H),4.60 (d, 1H, J= 8.7 Hz), 3.22-4.36 (m, 12H), 3.78 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (m, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.17-1.29 (m, 20H), 0.87 (t, 3H, J= 6.9 Hz). MS FAB: 912 (M+Na)$^+$.

6.15.
Dodecylcarbamyolmethyl 2-acetamido-6-O-(2'-acetamido-3',4',6'-tri-O-acetyl-2'-deoxy-β-D-glucopyranosyl)-4-O-acetyl-2-deoxy-3-O-[carboxymethyl]-α-D-glucopyranoside (20)

Compound (19) (250 mg, 0.28 mmol) is treated with aqueous 0.1M KOH solution (4.2 mL, 0.42 mmol) in dioxane (12 mL) as in compound (12). After workup, compound (20) is obtained (230 mg,94%) as a solid. TLC (20% methanol/ methylene chloride) Rf 0.45. ^{1}H NMR (300 MHz, $CDCL_3$) δ 8.40 (m, 1H), 7.43(m, 1H), 6.42 (m, 1H), 4.87-5.29 (m, 5H), 3.81-4.48 (m, 13H), 3.70 (s, 3H), 3.23 (m, 2H), 2.11 (s, 3H), 2.08 (s, 3H), 2.03 (s, 6H), 2.02 (m, 6H), 1.25 (m, 20H), 0.87 (t, 3H).

6.16.
Carboxymethyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (22)

Compound (21) (740 mg, 177 mmol) is treated with sodium periodate (1.5g 7.08 mmol) and ruthenium (III) chloride as in compound (10) to give compound (22) as a solid (540 mg, 70%). TLC (10% methanol/ methylene chloride) Rf 0.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 5.36 (d, 1H), 5.08 (m, 1H), 3.79-4.36 (m, 9H), 3.78 (s, 3H), 2.10 (s, 3H), 2.09 (s, 6H).

6.17.
Dodecylcarbamoylmethyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-3-O-[methoxycarbonylmethyl]-α-D-glucopyranoside (23)

Compound (22) (540 mg, 1.2 mmol) is treated with 1-hydroxybenzotriazole (195 mg, 1.44 mmol), 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate (762 mg, 1.8 mmol) and dodecylamine (267 mg, 1.44 mmol) as in compound (11). After silica gel column and eluting with ethyl acetate pure compound (23) is obtained (450 mg, 63%) as a solid. TLC (10% methanol/methylene chloride) Rf 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 6.53 (m, 1H), 5.41 (d, 1H, J = 2.4Hz), 5.06 (m, 1H), 3.79-4.40 (m, 9H), 3.80 (s, 3H), 3.27 (m, 2H), 2.13(s, 3H), 2.09 (s, 3H), 2.07(s, 3H), 1.98-1.20 (m, 20H), 0.87 (t, 3H J=6.3Hz). MS FAB: 625 $(M+Na)^+$.

6.18.
Dodecylcarbamoylmethyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-3-O-[carboxy methyl]-α-D-glucopyranoside (24)

Compound (23) (150 mg, 0.5 mmol) is treated with an 0.1M aqueous solution of KOH(3.8 mL, 0.38 mmol) in dioxane (10 mL) as for compound (12), after workup to give compound (24) (148 mg, 100%) as a solid. TLC (10% methanol/methylene chloride) Rf 0.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83-5.15 (m, 2H), 5.06 (m, 1H), 3.80-4.38 (m, 9H), 3.15-3.39 (m, 2H), 2.13(s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.25 (m, 20H), 0.85 (t, 3H J=6.3Hz). MS FAB 611 $(M+Na)^+$, 633 $(M+2Na-H)^+$.

6.19.
Dodecylcarbamoylmethyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-3-O-[pentafluoropheoxycarbonylmethyl]-α-D-glucopyranoside (25)

Compound (24)(300 mg, 0.5 mmol) is treated with pentafluoro phenol (101 mg, 0.55 mmol) and 1-

cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (282 mg, 0.65 mmol), as for compound (13). After workup compound (25) is obtained (450 mg, 100%). TLC (10%methanol/ methylene chloride) Rf 0.7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, 1H, J = 4.5Hz), 6.40 (m, 1H), 5.24 (d, 1H, J = 3.6Hz), 5.19 (m, 1H), 4.56-4.78 (m, 2H), 3.86-4.19 (m, 7H), 3.24-3.30 (m, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.25 (m, 20H), 0.85 (t, 3H J=6.6Hz). MS FAB: 777 $(M+Na)^+$.

6.20.
Allyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-[carbonylmethyl]-α-D-glucopyranoside (47)

Compound (14) (1.0 g, 2.4 mmol) is suspended in methanol (40 mL). To this suspension is added potassium hydroxide (403 mg, 7.2 mmol) and water (0.1 mL), stirred for 4h at room temperature. This basic mixture is neutralized with amberlite H^+ and filtered. After evaporating the solvent, crystalline product is obtained (100%). TLC(10% methanol/methylene chloride) Rf 0.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.48 (m, 5H), 7.18 (d, 1H, J = 6.6Hz), 5.81-5.94 (m, 1H), 5.57 (s, 1H), 5.20-5.32 (m, 2H),5.12 (d, 1H, J = 3.6Hz), 4.38 (ABq, 2H), 3.76-4.50 (m, 8H), 2.06 (s, 3H).

6.21.
Allyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-[pentafluorophenoxycarbonylmethyl]-α-D-glucopyranoside (48)

Compound (47) (1.0 g, 2.4 mmol) is treated with pentafluoro phenol (497 mg, 2.7 mmol) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (1.14, 2.7 mmol), as for compound (13). After workup compound (48) is obtained (1.4 g 100%) as a solid. TLC (10% methanol/ methylene chloride) Rf 0.75. ^{1}H NMR (300 MHz, $CDCL_3$) δ 7.36-7.50 (m, 5H), 6.37 (d, 1H, J = 7.2Hz), 5.82-5.94 (m, 1H),

5.60 (s, 1H), 5.23-5.31 (m, 2H), 5.19 (d, 1H J=2.4Hz), 4.77 (ABq, 2H), 3.73-4.31 (m, 8H), 2.06(s, 3H).

6.22.
Methyl 2(S)-O-Trifluoromethanesulfonyloxypropiolate (4)

Trifluoromethanesulfonyl anhydride (13.3 mL, 79 mmol) is added dropwise to a stirred solution of anhydrous pyridine (6.7 mL, 83 mmol) in anhydrous dichloromethane (250 mL) at -40 °C to give a white suspension. A solution of methyl-2(S)-hydroxypropiolate (8.2 g, 79 mmol) in dichloromethane (15 mL) is then added to the reaction mixture at -40 °C, and the stirred reaction mixture is allowed to warm to room temperature over 1 h. The white precipitate is filtered off, and the filtrate is concentrated below 30 °C on a rotary evaporator to give a brown liquid. This liquid is passed through a 15 cm plug of silica (eluting with P_2O_5-dried hexane, 250 mL) and concentrated to give the crude product as a pale yellow liquid (9.8 g). Vacuum distillation gives pure methyl-(S)-2-O-trifluoromethanesulfonyl-propiolate (4)(7.8 g, 33 mmol, yield 42%) as a colorless mobile liquid (b.p. 60 °C, 10 torr). ^1H NMR (300 MHz, $CDCl_3$) δ 5.22(q, 1H), 3.83 (s, 3H), 1.69 (d, 2H).

6.23.
Allyl 4,6-O-benzylidene-3-O-[1'(R)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (5a) and Allyl-4,6-O-benzylidene-3-O-[1'(S)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (5b)

A stirred suspension of alcohol (3)(9.06 g, 26 mol) in anhydrous dichloromethane (150 mL) is heated at 40 °C for 10 min under argon and then treated with 95% sodium hydride (0.78 g, 32.5 mmol). After 5 min, triflate (4)(9.2g, 39 mmol) is added cautiously over 15 min causing a vigorous exotherm and evolution of

hydrogen. After a further 20 min, the reaction mixture is cooled and poured into water (100 mL). The organic layer is separated, washed with water (50 mL), dried over Na_2SO_4 and evaporated to give a white solid (15 g). The crude product is purified by flash chromatography on silica (250 g) using a gradient elution 10 → 20% ethyl acetate-dichloromethane to give firstly allyl-4,6-O-benzylidene-3-O-[1'(R)-(methylcarboxy)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (**5a**) (6.1 g, 14 mmol, yield 54%) and then allyl-4,6-O-benzylidene-3-O-[1'(S)-(methylcarboxy)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (**5b**) (1.65 g, 3.8 mmol, yield 14.5%), both as white solids.

Spectral data for **5a**: TLC (30% EtOAc-hexane) Rf 0.55. IR (KBr disc): 3207, 1736, 1632, 1547, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.37 (m, 5H, Ph-H), 5.88 (m, 1H, allyl C-H), 5.58 (s, 1H, CH-Ph), 5.32(d, 1H, J=3.3 Hz, H-1), 5.30-5.23 (two d, 2H, $=CH_2$), 4.53 (q, 1H, O-CH(Me)CO_2Me), 4.28-3.66 (m, 12H including s,3H at 3.75), 2.06 (s, 3H, NHAc), 1.42 (d, 3H,O-CH(Me)CO_2Me). FAB MS: 458 $(M+Na)^+$.

Spectral data for **5b**: TLC (30% EtOAc-hexane) Rf 0.38. IR (KBr disc): 3280, 1752, 1640, 1560, 1375, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.5-7.35 (m, 5H, Ph-H), 5.89 (m, 1H, allyl C-H), 5.58 (s, 1H, CH-Ph), 5.78 (br d, 1H, NH), 5.46-5.20 (two d, 2H, $=CH_2$), 4.90 (d, 1H, J=3.6 Hz, H-1), 4.53 (q, 1H, O-CH(Me)CO_2Me), 4.33-3.63 (m, 10H), 3.24 (s, 3H, CO_2Me), 2.02 (s, 3H, NHAc), 1.31 (d, 3H,O-CH(Me)CO_2Me). FAB MS: 458 $(M+Na)^+$.

6.24.
Allyl 3-O-[1'(R)-(Methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (6)

A stirred solution of the benzylidene acetal (5a) (8.0 g, 18.4 mmol) in 75% AcOH-H_2O (100 mL) is heated at 55 °C for 14 h. The reaction mixture is concentrated under reduced pressure at 50 °C, and the residue is dried by azeotropic distillation from toluene (2 x 100 mL). The crude product is preadsorbed on silica (25 g) and purified by flash chromatography on silica (eluant 10 → 20% ethanol-dichloromethane) to give allyl-3-O-[1'(R)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (6) (4.65 g, 13.4 mmol, yield 83%) as an oil. TLC (10% MeOH-CH_2Cl_2) Rf 0.52. IR (neat): 3336, 2929, 1734, 1654, 1548, 1226, 1133, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 7.64 (d, 1H, NH), 5.85 (m, 1H), 5.28-5.14 (m, 3H), 4.72 (q, 1H), 4.14-3.55 (m, 13H including s, 3H at 3.76), 2.04 (s, 3H), 1.41 (d, 3H). FAB MS 370 (M+Na)$^+$.

6.25.
2-Methyl-4,5-(tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-Δ^2- oxazoline (7)

The 2-deoxy-2-acetamido-D-glucopyranoside (49.0 g, 222 mmol) is stirred in acetyl chloride (90 mL, 1.261 mol) for 18 h at r.t. The clear red oil is diluted with ethanol-free chloroform (400 mL), stirred for 1 h at r.t. and then poured onto ice (700 mL). The organic layer is separated, washed quickly with ice cold saturated aqueous $NaHCO_3$ (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure to a volume of about 50 mL. Diethyl ether (400 mL) is added, and the product, 3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-α-D-glucopyranosyl chloride (58 g, yield 71%) is collected as off-white crystals. The chloride (40 g, 109 mmol), tetraethylammonium bromide (22.9 g, 109 mmol) and anhydrous sodium bicarbonate (18.3 g, 218 mmol) are stirred in anhydrous acetonitrile (80 mL) until

evolution of CO_2 gas ceases (ca. 30 min). The reaction mixture is filtered, and the filtrate evaporated. The residue is dissolved in dichloromethane (300 mL), washed with water (4 x 50 mL) and re-evaporated. The residue is taken up in diethyl ether (250 mL) and stored at -20 °C for 3 h. Some colorless crystals of an impurity, 1,3,4,6-tetra-O-acetyl-2-deoxy-2-acetamido-D-glucopyranoside (2.5 g), are removed by filtration. The product, 2-methyl-4,5-(tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-Δ2-oxazoline (7) (29 g, 88 mmol, yield 81%), is obtained by evaporation of the filtrate as a golden yellow oil. TLC (Et_2O) Rf 0.24. ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, 1H), 5.23 (t, 1H), 4.92 (dd, 1H), 4.2-4.1 (m, 3H), 3.60 (quintet, 1H), 2.04 (m, 12H).

6.26.
Carboxymethyl 4,6-O-Benzylidene-3-O-[1'(R)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (26)

The carboxylic acid (26) is prepared in a similar manner to compound (10) by the reaction of compound (5a) (1.28 g, 2.94 mmol) with sodium periodate (2.83 g, 13.24 mmol) and ruthenium trichloride hydrate (12 mg). The crude product, an oil (1.8 g), is used without further purification in the next step. TLC (10% MeOH-DCM) Rf 0.05. ^1H NMR (300 MHz, $CDCl_3$) δ 7.9 (d, 1H), 7.4 (m, 5H), 5.54 (s, 1H), 5.4 (d, 1H), 4.5 (q, 1H), 4.3-3.6 (m, 12H), 2.05 (s, 3H), 1.4 (d, 3H).

6.27.
Dodecylcarbamoylmethyl 4,6-O-Benzylidene-3-O-[1'(R)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (27)

A solution of the crude acid (26) (1.8 g, 2.9 mmol), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (WSCDI) (1.49 g, 3.53 mmol), HOBt (0.476 g, 3.53 mmol) and dodecylamine (0.598 g,

3.23 mmol) in dichloromethane (100 mL) is stirred at r.t. for 15 h. The solvent is evaporated, and the residue is taken up in EtOAc (100 mL), washed with 2N HCl (50 mL), sat'd aq. $NaHCO_3$ (50 mL) and then dried over Na_2SO_4. Evaporation under reduced pressure gives a white solid (4.0 g), which is flash chromatographed on silica eluting with 3% MeOH-DCM to give the title compound (27) (0.97 g, yield 54% over two steps) as a white solid. TLC (5% MeOH-DCM) Rf 0.32. ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H), 7.46-7.36 (m, 5H), 6.00 (t, 1H), 5.59 (s, 1H), 5.46 (d, 1H), 4.55 (q, 1H), 4.26 (m, 1H), 4.12-3.98 (dd, 2H), 3.80-3.71 (m, 8H including s at 3.77), 3.27 (m, 2H), 2.08 (s, 3H), 1.62-1.43 (m, 2H), 1.44 (d, 3H), 1.4-1.25 (m, 18H), 0.87 (t, 3H). FAB MS: 643 $(M+Na)^+$.

6.28.
Dodecylcarbamoylmethyl 4,6-O-benzylidene-3-O-[1'(R)-(carboxy)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (28)

A solution of methyl ester (27) (0.97g, 1.56 mmol) and sodium hydroxide (187 mg, 4.69 mmol) is stirred at r.t. in 1:1 THF-MeOH (50 mL) for 14 h. The solution is acidified with Dowex 50 H^+ resin, filtered and evaporated to give a yellow-white solid. TLC (10% MeOH-DCM) Rf 0.09. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 5.54 (s, 1H), 5.24 (d, 1H, J = 1.8 Hz), 4.43 (q, 1H, J = 7.2 Hz), 4.21 (m, 1H), 4.07-3.86 (two d, 2H, J = 15.6 Hz), 3.8-3.6 (m, 7H), 3.19 (m, 2H), 1.99 (s, 3H), 1.47 (m, 2H), 1.39 (d, 3H, J = 7.2 Hz), 1.28-1.91 (m, 18H), 0.81 (t, 3H, J = 6.6 Hz). FAB MS: 629 $(M+Na)^+$ and 651 $(M+2\ Na-H)^+$.

6.29.
Dodecylcarbamoylmethyl 4,6-O-benzylidene-3-O-[1'(S)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (29)

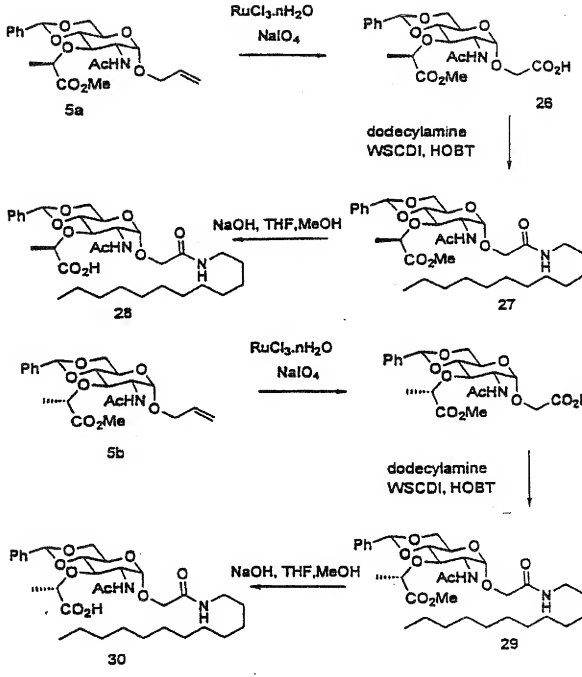
The allyl group of compound (**5b**) (2.00 g, 4.60 mmol) is converted to a methylene carboxy group using sodium periodate (4.43 g, 20.70 mmol) and ruthenium trichloride hydrate (17 mg) as in the preparation of compound (**10**) to give the crude acid as a greenish white solid. TLC (10% MeOH-DCM) Rf baseline. The crude acid is then allowed to react with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (2.34 g, 5.52 mmol), HOBt (0.745 g, 5.52 mmol) and dodecylamine (0.936 g, 5.06 mmol) as in the preparation of compound (**27**). After workup and chromatography, the amide (**29**) (0.8 g, 1.29 mmol, yield 28%) is obtained as a white solid. TLC (5% MeOH-DCM) Rf 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 5H), 6.38 (br t, 1H), 6.22(d, 1H), 5.46 (s, 1H), 5.08 (d, 1H), 4.28-3.67 (m, 10H), 3.28 (s and m, 5H), 2.05 (s, 3H), 1.53 (m, 2H), 1.35 (d, 3H), 1.35-1.24 (m, 18H), 0.87 (t, 3H). FAB MS: 643 $(M+Na)^+$.

6.30.
Dodecylcarbamoylmethyl 4,6-O-benzylidene-3-O-[1'(S)-(carboxy)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (30)

A solution of methyl ester (**29**) (0.80g, 1.29 mmol) and sodium hydroxide (154 mg, 3.87 mmol) is stirred at r.t. in 1:1 THF-MeOH (50 mL) for 14 h. The solution is acidified with Dowex 50 H^+ resin, filtered and evaporated to give the carboxylic acid (**30**) as a white solid. TLC (10% MeOH-DCM) Rf 0.09. ^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD) δ 7.62 (br t, 1H), 7.40-7.27 (m, 5H), 5.46 (s, 1H), 4.73 (d, 1H, J = 3.9 Hz), 4.27-4.10 (m, 4H), 3.88 (d, 1H), 3.8-3.65 (m, 4H), 3.21 (m, 2H), 2.00 (s, 3H), 1.49 (m, 2H), 1.25 (d, 3H, J = 7.6 Hz), 1.26-1.20 (m, 18H), 0.83 (t, 3H, J = 6.6 Hz). FAB MS: 629 $(M+Na)^+$ and 651 $(M+2Na-H)^+$.

6.31.
Allyl 4,6-O-benzylidene-3-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (31)

Alcohol (3) (40.5 g, 106.7 mmol) is azeotroped with toluene (100 mL) then dissolved in anhydrous DMF (700ml) under argon. 95% NaH (3.23 g, 128.1 mmol) is added portionwise to the stirred solution over 5 min. After the evolution of hydrogen gas has ceased, benzyl bromide (15.3 mL, 128.1 mmol) is added in one portion and the reaction mixture is stirred overnight at R.T under argon. The reaction mixture is poured into water (1 L) causing the crude product to precipitate as a white solid. This is collected by filtration, and the filter-cake is washed with water (3 x 500 mL) then hexane (2 x 200 mL). The wet filter-cake is redissolved in DCM (1 L), washed with brine (100 mL), dried over Na_2SO_4 and evaporated to give the benzyl ether (31)(42.33g, yield 90.3%) as an off-white solid. TLC (10% MeOH-DCM) Rf 0.48. ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.27 (m, 5H), 5.85 (m, 1H), 5.60 (s, 1H), 5.36 (br d, 1H), 5.23 (d, 1H), 5.20 (d, 1H), 4.92 (d, 1H), 4.86 (d, 1H, J = 3.6Hz, H-1), 4.63 (d, 1H), 4.33-3.69 (m, 8H), 1.92 (s, 3H, NHAc). FAB MS: 462 $(M+Na)^+$.



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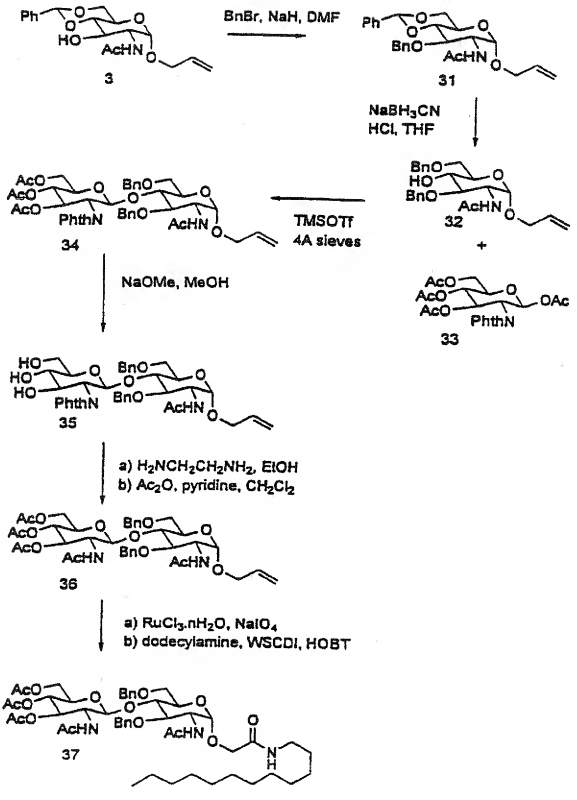
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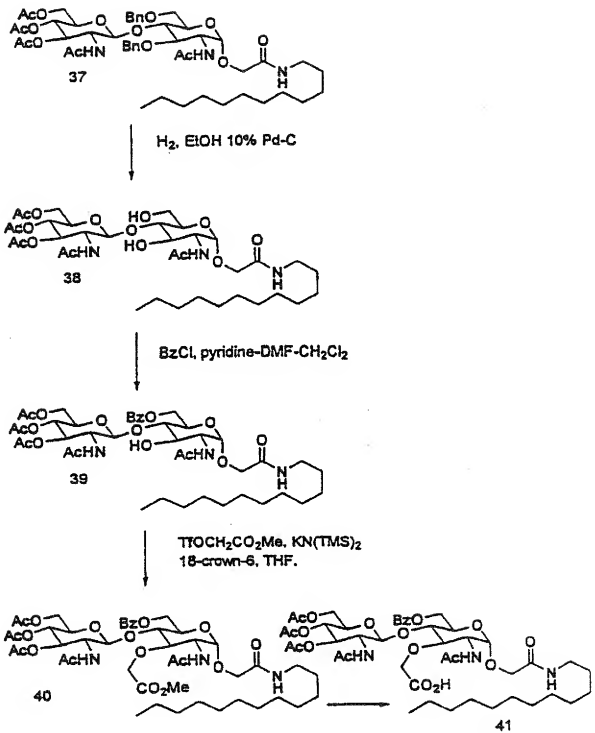
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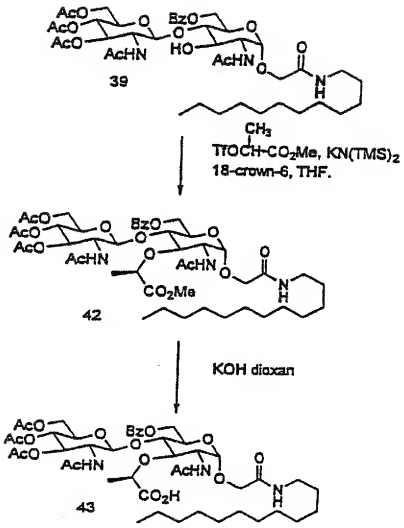
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CO2Me
42
KOH dioxan
CO2H
43

6.32.
Allyl 3,6-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (32)

Benzylidene acetal (31) (42.33 g, 96.4 mmol) is azeotroped once with toluene (150 mL) then dried under vacuum in a 2L flask. 3A powdered molecular sieves (65 g), sodium cyanoborohydride (54.5 g, 868 mmol) and anhydrous THF (800 mL) are added under argon. The stirred suspension is cooled to 0 °C and 1N HCl in diethyl ether (800 mL) is added by cannula over 40 min. The milky solution is stirred at r.t. until the reaction is complete by TLC (10% MeOH-CH_2Cl_2) at 2 h. 2N HCl (aq) (300 mL)is added, the reaction mixture is shaken and then ethyl acetate (1 L) is added. The organic layer is separated, concentrated under reduced pressure to a yellow liquid (200 mL) then redissolved in dichloromethane (1 L). Ethanolamine (70 mL) is added, the reaction mixture is stirred for 20 min at r.t. and then washed with water (500 mL), 2N HCl(aq) (2 x 500 mL) and brine (100 mL). Drying over Na_2SO_4 and evaporation gives the title compound (32) (41 g, yield 95%) as an orange oil which crystallizes over several days to an amorphous white solid. TLC (10% MeOH-CH_2Cl_2) Rf 0.29. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.85 (m, 1H), 5.48 (br d, 1H), 5.25 (dt, 1H), 5.20 (dt, 1H), 4.82 (d, 1H, J = 3.9Hz, H-1), 4.73 (q, 2H), 4.58 (q, 2H), 4.28-4.16 (m, 2H), 3.95 (dd, 1H), 3.80-3.56 (m, 6H), 1.91 (s, 3H, NHAc). FAB MS: 464 $(M+Na)^+$.

6.33.
2-Phthalimido-2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (33)

Compound (33) (23 g, 48.2 mmol) is prepared according to the method of R.U. Lemieux T. Takeda, and B.Y. Chang, Am. Chem. Soc. Symp. 39, 90, (1976). White crystalline solid. TLC (50% EtOAc-

hexane) Rf 0.24. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.74 (m, 2H), 6.49 (d, 1H, J = 9.0 Hz), 5.87 (dd, 1H, J = 9.3 and 10.8 Hz), 5.20 (t, 1H, J = 9.9 Hz), 4.46 (dd, 1H, J = 9.0 and 10.8 Hz), 4.36 (dd, 1H, J = 4.8 and 12.3 Hz), 4.13 (dd, 1H, J = 2.1 and 12.3 Hz), 4.01 (ddd, 1H), 2.10, 2.02, 1.98, 1.85 (4s, 12H, 4 x OAc).

α/β ratio <1/20 by ^{1}H NMR .

6.34.
Allyl 4-O-(2'-phthalimido-2'-deoxy-3',4',6'-tri-O-acetyl-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (34)

Compound (32) (14.8 g, 33.6 mmol) and compound (33) (22.4 g, 46.9 mmol) are azeotroped together in dry toluene (120 mL) then activated powdered 4A sieves are added to the residue and the mixture is resuspended in dry dichloromethane (500ml). The suspension is stirred 1 h under argon then TMSOTf (35ml) is added to the stirred suspension followed by a second 10ml portion after 30 min and a further 10 mL portion at 4 h. The reaction is stopped after 4 h 30 min by addition of triethylamine (70 mL). The black solution is filtered through a celite pad which is then washed with dichloromethane (300 mL). The combined filtrates are washed with water (2 x 300 mL), 2N HCl (aq) (2 x 200 mL) and once with brine (200 mL) then dried (Na_2SO_4) and evaporated to a brown solid (33 g). Flash chromatograph on silica (650 g) using a gradient elution : 50%→ 100% EtOAc:hexane affords reactant (33) (4.2 g) followed by the title compound (17.4 g, yield 60.5%) as a yellow oil. TLC (EtOAc) Rf 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H, NPhth-H), 7.72 (m, 2H, NPhth-H), 7.35-7.25 (m, 10H, 2 x PhH), 5.77 (m, 1H, Allyl =CH-), 5.73 (dd, 1H, J = 8.7 and 10.5 Hz, H-4'), 5.51 (d, 1H, J = 8.4 Hz, H-1'), 5.21 (br d, 1H, J = 9.0 Hz, N-H), 5.15-5.07 (m, 3H, allyl =CH_2, H-3'), 4.90 (d,

1H, J = 12.3 Hz, CH_aHPh), 4.78 (d, 1H, J = 3.6 Hz, H-1), 4.61 (d, 1H, J = 12.3 Hz, CH_aHPh), 4.48 (2d, 2H, J = 11.6 Hz, CH_2Ph), 4.30 (dd, 1H, J = 8.7 and 10.8 Hz, H-2'), 4.2-4.07 (m, 3H), 3.98 and 3.82 (two dd, 2H, H-6_a, H-6_B), 3.59-3.35 (m, 5H), 1.98, 1.94, 1.82, and 1.78 (4s, 12H, 3 x OAc, NHAc). FAB MS: 881 (M+Na)⁺.

6.35
Allyl 4-O-(2'-phthalimido-2'-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (35)

Compound (34) (17.4 g, 20.3 mmol)is dried by azeotropic distillation from toluene (50 mL) then dissolved in dry methanol (150 mL) under argon. Sodium methoxide (1.1 g) is added and the reaction mixture is stirred at r.t. for 1 h (reaction complete by TLC: 10%MeOH-DCM). Subsequently, 1N HCl in diethyl ether (15 mL) is added to adjust the pH of the reaction mixture to pH 5, and concentration gives the title compound (35) as a brown foam (20 g). TLC (20% MeOH-DCM) Rf 0.58. ^{1}H NMR (300 MHz, MeOH) δ 7.8 (m, 2H, NPhth-H), 7.7 (m, 2H, NPhth-H), 7.35-7.25 (m, 10H, 2 x PhH), 5.75 (m, 1H, Allyl =CH-), 5.37 (d, 1H), 5.3 (m, 3H), 4.90 (d, 1H), 4.7(d, 1H, H-1), 4.6-4.45 (m, 3H), 4.3-3.1 (m, 17H), 1.8 (s, 3H, NHAc). FAB MS: 755 (M+Na)⁺.

6.36.
Allyl 4-O-(3',4',6'-tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (36)

Crude compound (35)(20 g, 20.3 mmol) is heated with 4 equivalents of ethylene diamine (4.86 g, 81.2 mmol) in ethanol at 75 °C for 16 h under argon. The reaction mixture is evaporated under reduced pressure at 65 °C and then dried by azeotropic distillation from toluene (100 mL) to give the free amine as a brown solid. This solid is redissolved in dichloromethane

(60 mL) containing acetic anhydride (35 mL), pyridine (60 mL) and 4-dimethylaminopyridine (0.2 g) causing the temperature of the reaction mixture to rise to 45 °C. The reaction mixture is stirred at r.t. for 24 h, then diluted with dichloromethane (400 mL) and washed with ice-cold water (2 x 400 mL), ice-cold sodium bicarbonate (2 x 200 mL), 2N HCl (2 x 200 mL), then brine (100 mL). The solution is dried over Na_2SO_4 and evaporated to a brown solid (15.93 g). Flash chromatography on silica using a solvent elution gradient of: 2% → 5% MeOH-DCM gives the title compound (12.58 g, yield 78%) as a white solid. TLC (10% MeOH-CH_2Cl_2) Rf 0.57. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.22 (m, 10H, 2 x PhH), 5.80 (m, 1H, Allyl =CH-), 5.51 (d, 1H, J = 8.4 Hz, H-1'), 5.25-5.15 (m, 2H, allyl $=CH_2$), 5.09 (br d, 1H, J = 9.0 Hz, N-H), 5.02-4.78 (m, 5H), 4.53 (d, H, J = 9.8 Hz) ,4.48 (d, H, J = 12.4 Hz) , 4.36 (d, 1H, J = 9.8 Hz), 4.32 (d, 1H, J = 5.9 Hz), 4.18 (dd, 1H, J = 4.6 and 12.2 Hz) 4.12 (m, 1H), 4.08-3.82 (m, 5H), 3.64 (d, 2H), 3.58-3.44 (m, 3H) 2.01, 1.99, 1.92 (3s, 9H, 3 x OAc), 1.73 and 1.72 (2s, 6H, 2 x NHAc). FAB MS: 793 $(M+Na)^+$.

6.37.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (37)

Sodium periodate (0.61 g, 2.83 mmol) is added to a vigorously stirred ice-cold suspension of compound (36) (0.49 g, 0.69 mmol) and ruthenium trichloride hydrate (3 mg, 1 x 10^{-5} M) in a three-component solvent: acetonitrile (1 mL), carbon tetrachloride (1 mL) and water (1 mL). After 10 min, the stirred reaction mixture is allowed to warm to room temperature over 2 h. The reaction mixture is diluted with dichloromethane (50 mL), filtered through celite, and

the filtrate is evaporated to a yellow-brown solid (0.43g). ^1H nmr ($CDCl_3$) indicates that this solid is mainly the 1-carboxymethyl derivative contaminated with a small amount of 1-formylmethyl derivative resulting from incomplete oxidation. FAB MS (for the carboxylic acid): 811 $(M+Na)^+$, 833 $(M+2Na-H)^+$. The mixture is used without further purification in the next step.

A solution of the crude carboxylic acid (0.43 g, c.a. 0.54 mmol), dodecylamine (110 mg, 0.59 mmol), 1-hydroxybenzotriazole (80 mg, 0.59 mmol) and dicyclohexylcarbodiimide (DCC)(133 mg, 0.65 mmol) in dichloromethane (15 mL) is stirred for 20 h at r.t. The reaction mixture is filtered, diluted with dichloromethane (40 mL) and washed with 2N HCl (2 x 20 mL), sodium bicarbonate solution (2 x 20 mL) and brine (20 mL), then dried (Na_2SO_4) and evaporated to a yellow-brown solid (0.52 g). Flash chromatography on silica (15 g) using a solvent elution gradient of: CH_2Cl_2 → 3% MeOH-CH_2Cl_2, gives the title compound (37) (380 mg, 0.39 mmol; yield 58%) as a white solid. TLC (10% MeOH-CH_2Cl_2) Rf 0.57. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.25 (m, 10H, 2 x PhH), 6.38 (br t, 1H, NH), 5.34 (br d, 1H), 5.01 (d, 1H, J = 3.4 Hz, H-1), 5.00 (t, 1H, J = 9.8 Hz), 4.88-4.77 (m, 4H), 4.68 (d, 1H, J = 9.5 Hz), 4.54 (d, H, J = 12.5 Hz), 4.38-4.22 (m, 3H), 4.05-3.85 (m, 6H), 3.64-3.46 (m, 5H), 3.22 (m, 2H), 2.02, 1.99, 1.96 (3s, 9H, 3 x OAc), 1.75 and 1.73 (2s, 6H, 2 x NHAc), 1.47 (m, 2H), 1.23 (m, 18H), 0.86 (t, 3H, J = 6.3 Hz). FAB MS: 978 $(M+Na)^+$.

6.38.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-2-deoxy-2-acetamido-α-D-glucopyranoside (38)

A solution of compound (37) (4.2 g, 4.4 mmol) in ethanol (50 mL) and 10%Pd/C (0.75 g) is shaken at r.t. in a Parr hydrogenation apparatus for 3 days under 50

psi of hydrogen gas. The product which crystallizes from the reaction mixture is redissolved by addition of dichloromethane (300 mL), and the catalyst removed by filtration through a celite pad. Evaporation gives a white solid (~5 g). This solid is purified by flash chromatography on silica using a solvent elution gradient of: 5% → 15% MeOH-CH_2Cl_2 to afford the title compound (38) (2.3 g, yield 67%) as a white solid. TLC (10% MeOH-CH_2Cl_2) Rf 0.21. ^1H NMR (300 MHz, d_6-DMSO) δ 7.97 (2d, 2H, 2 x NH), 7.72 (br t, 1H, NH), 5.06 (t, 1H, J = 10.0 Hz), 4.83 (t, 1H, J = 9.8 Hz), 4.71 (d, 1H, J = 8.6 Hz, H-1'), 4.60 (d, 1H, J = 3.4 Hz, H-1), 4.60 (m, 1H), 4.36 (m, 1H), 4.2-2.95 (m, 3H), 15H), 1.99, 1.96, 1.90, 1.83, 1.77 (5s, 15H, 3 x OAc, 2 x NHAc), 1.40 (m, 2H), 1.22 (m, 18H), 0.83 (t, 3H, J = 7.1 Hz). FAB MS: 798 (M+Na)$^+$.

6.39.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-6-O-benzoyl-2-deoxy-2-acetamido-α-D-glucopyranoside (39)

Benzoyl chloride (0.75 mL, 6.5 mmol) is added to a stirred solution of compound (38) (2.8 g, 3.61 mmol) and DMAP (0.2 g) in (4:1) pyridine-dichloromethane (100 mL) at -20 °C. The reaction mixture is allowed to warm up to r.t. over 1 h. The reaction mixture is then recooled to -20 °C, and DMF (20 mL) is added, causing the milky solution to become clear and bright yellow in colour. The reaction is allowed to warm up to r.t. over 1 h, then diluted with dichloromethane (300 mL) and washed with water (300 mL), 2N HCl (4 x 200 mL), sodium bicarbonate (100 mL) and brine (100 mL). The solution is dried over Na_2SO_4. Methanol (30 mL) is added, and the solution is filtered and evaporated to provide a white solid (4 g). Flash chromatography on silica, eluant: 5% → 15% MeOH-CH_2Cl_2 gives the title

compound (39) (1.6 g, yield 50.5%) as a white solid and also the diol (38) (1.1 g, 39% recovery). Compound (39) TLC (5% MeOH-CH_2Cl_2) Rf 0.27. ^1H NMR (300 MHz, 2:1 $CDCl_3$-CD_3OD) δ 7.96 (d, 2H, J = 7.3 Hz, Bz-H_o), 7.54 (t, 1H, J = 7.3 Hz, Bz-H_p), 7.37 (t and m, 4H, Bz-Hm, 2 x NH), 5.09 (t, 1H, J = 9.8 Hz, H-4'), 4.92 (t, 1H, J = 9.8 Hz, H-3'), 4.74 (d, 1H, J = 3.4 Hz, H-1), 4.57 (d, 1H, J = 8.5 Hz, H-1'), 3.85 (br s, 2H), 4.15-3.98 (m, 7H), 3.88-3.72 (m, 4H), 3.48 (dd, 1H, J = 8.3 and 9.8 Hz, H-2'), 3.17 (q, 2H, J = 6.8 Hz), 2.00, 1.95, 1.94, 1.94, 1.87 (5s, 15H, 3 x OAc, 2 x NHAc), 1.44 (m, 2H), 1.23-1.18 (m, 18H), 0.80 (t, 3H, J = 7.3 Hz). FAB MS: 902 $(M+Na)^+$.

6.40.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-Tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-6-O-benzoyl-3-O-methoxycarbonylmethyl-2-deoxy-2-acetamido-α-D-glucopyranoside (40)

To a stirred solution of compound (39) (300 mg, 0.34 mmol) and 18-crown-6 in dry THF (30 mL) at 50 °C under argon is added a 0.5 M solution of potassium hexamethyldisilazide (1.7 mL, 0.85 mmol) in toluene. The reaction mixture is stirred for 10 min then methyl 2-O-trifluoromethanesulphonyloxyacetate (prepared from methyl glycolate in a similar manner to compound (4)) (300 mg, 1.36 mmole) is added to it. The reaction mixture is stirred for 3 h at 50 °C then quenched with 2 N HCl (0.5 mL). Evaporation gives a yellow oily residue which is partitioned between dichloromethane (75 mL) and water (70 mL), dried (Na_2SO_4) and evaporated. Flash chromatography on silica using a solvent eluant gradietn of 2% → 10% MeOH-DCM gives an upper fraction (80 mg), TLC (5% MeOH-DCM) Rf 0.35, and a lower fraction co-running with compound (39) (120 mg), TLC (5% MeOH-DCM) Rf 0.25. FAB MS on the upper fraction gives mass peaks at 974 $(M+Na)^+$ and 1046

(dialkylated product + Na)⁺. No starting material is found in this upper fraction. FAB MS on the lower fraction gives mass peaks at 934 (M+Na-Ac)⁺ and 902 (starting material + Na)⁺.

6.41.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-6-O-benzoyl-3-O-carboxymethyl-2-deoxy-2-acetamido-α-D-glucopyranoside (41)

An 0.1M aqueous solution of potassium hydroxide (2.0 mL, 0.2 mmol) is added to a stirred ice-cold solution of compound (39) (120 mg, 0.12 mmol) in dioxan (15 mL), and the reaction mixture is stirred until the starting material is consumed (by TLC, 10% MeOH-DCM, ca. 4 h). The solution is neutralized with Amberlite H⁺ resin and evaporated. The residue is dried by azeotropic distillation from toluene (20 mL) to afford the crude title compound (41) (110 mg).

6.42.
Dodecylcarbamoylmethyl 4-O-(3',4'-Di-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-6-O-benzoyl-3-O-[1(R)-(methoxycarbonyl)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (42)

Compound (39) (100 mg, 0.114 mmol) is treated with a 0.5M solution of potassium hexamethyl disilazide in toluene (0.46 mL, 0.23 mmol) and methyl 2(S)-O-triflyl lactate (53 mg, 0.23 mmol) and 18-crown-6 (10 mg) in THF (30 mL) as in example (40) to give after workup and chromatography, the title compound as an yellow solid (60 mg). FAB MS: 946 (M+Na)⁺ and 902 (starting material +Na)⁺ [contaminant].

6.43.
Dodecylcarbamoylmethyl 4-O-(3',4',6'-Tri-O-acetyl-2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-6-O-benzoyl-3-O-[1(R)-(carboxy)ethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (43)

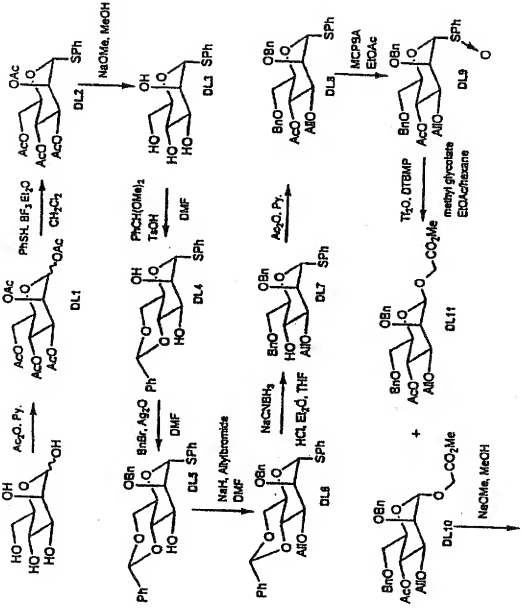
Compound (42) (50 mg) is acetylated with excess pyridine (1 mL) and acetic anhydride (0.5 mL) and DMAP (10 mg) for 2 h at room temperature. The reaction mixture is diluted with dichloromethane (20 mL) and washed three times with 2 N HCl (3 x 20 mL), dried over sodium sulfate and evaporated to a solid (50 mg). This solid is dried under high vacuum overnight, then hydrolysed as for compound (42) to give crude compound (43) as an oil (35 mg).

6.44.Carboxymethyl 4,6-O-benzylidene-3-O-[methoxycarbonylmethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (49)

Compound (14) is treated with sodium periodate and ruthenium (III) chloride as in compound (10). Column separation gives compound 49 (73%). ^{1}H NMR ($CDCl_3$) δ 7.95 (s, br, 1H), 7.50-7.40 (m, 2H), 7.40-7.30 (m, 3H), 5.563 (s, 1H), 5.434 (d, 1H, J = 3 Hz,) 4.412 (ABq, 2H), 4.35-4.15 (m, 3H), 3.95-3.85 (m, 2H), 3.750 (s, 3H), 3.80-3.65 (m, 1H), 2.130 (s, 3H).

6.45.Dodecylcarbamoylmethyl 4,6-O-benzylidene-3-O-[methoxycarbonylmethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (50)

Compound (49) is treated with 1-hydroxybenzotriazole, 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate and dodecylamine as in compound (11) to give compound (50) (50%). ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.45-7.35 (m, 2H), 7.35-7.30 (m, 3H), 6.52 (s, 1H), 5.539 (s, 1H), 5.369 (d, 1H, J = 2.1 Hz,) 4.404 (ABq, 2H), 4.25-4.20 (m, 1H), 4.025 (ABq, 2H), 3.85-3.80 (m, 2H), 3.737 (s, 3H), 3.80-3.65 (m, 2H), 3.30-3.15 (m, 2H), 2.044 (s, 3H), 1.60-1.45 (m, 2H), 1.35-1.15 (m), 0.837 (t, 3H, J = 6.6 Hz).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DMF
DL5
DL6
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DL7
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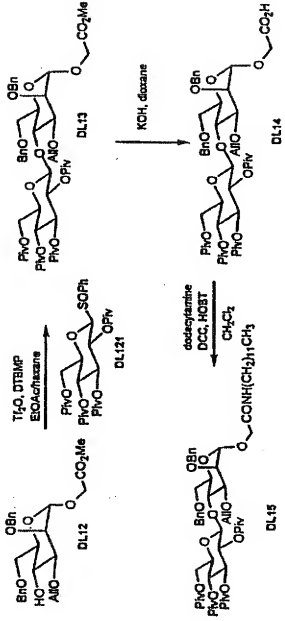
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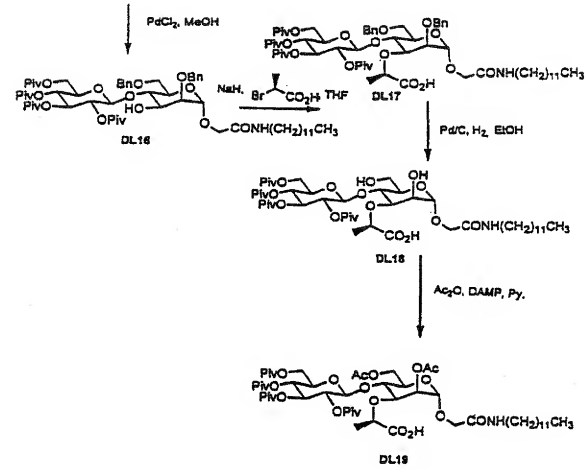
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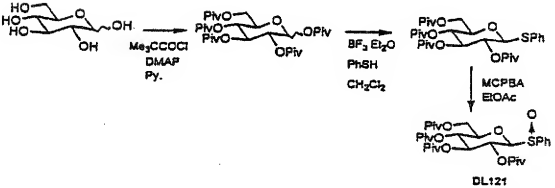
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6.46.Dodecylcarbamoylmethyl 4,6-O-benzylidene-3-O-[carboxymethyl]-2-deoxy-2-acetamido-α-D-glucopyranoside (51)

Compound (50) is dissolved in 1,4-dioxane and treated with 0.1M aqueous solution of potassium hydroxide as in the preparation of compound (12). Compound 51 is recovered in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 8.10 (s, br, 1H), 7.50-7.40 (m, 2H), 7.40-7.30 (m, 3H), 6.56 (s, br, 1H), 5.570 (s, 1H), 5.278 (d, 1H, J = 3.6Hz,) 4.419 (s, 2H), 4.260 (d, 1H, J = 5.7 Hz), 4.071 (ABq, 2H), 4.00-3.90 (m, 1H), 3.90-3.65 (m, 3H), 3.26 (m, 2H), 2.072 (s, 3H), 1.52 (m, 2H), 1.24 (m), 0.874 (t, 3H, J = 6.75 Hz). Fab MS: 637 (M-H+2Na)$^+$.

6.47.

α,β-D-Mannose pentaacetate (DL1)

To a stirred solution of D-mannose (75 g, 0.41 mol) and 4-N,N-dimethyaminolpyridine (5 g) in dry pyridine (700 mL) at 0 °C is added dropwise acetic anhydride (300 mL). The resulting solution is stirred at room temperature for 16 h. The solvent is removed by evaporation. The residue is dissolved in ethyl acetate (500 mL), washed with 1 M aquous HCl solution to pH 2. The organic layer is washed with saturated $NaHCO_3$ to pH 7, separated, dried (Na_2SO_4) and concentrated to give 160 g of DL1 (100%) as a white solid. TLC (ethyl acetate:hexane 2:3) Rf 0.34. ^{1}H NMR ($CDCl_3$) δ 6.10 (d, 0.8H, J = 1.2 Hz, H-1), 5.85 (d, 0.2H, J = 1.3 Hz, H-1), 5.50-5.10 (m, 3H), 4.60-4.00 (m, 3H), 2.17 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H).

6.48.
Phenyl 2,3,4,6-O-pentaacetyl-1-thio-D-mannopyranoside (DL2)

To a stirred solution of **DL1** (160 g, 0.41 mol) and thiophenol (49 g, 0.45 mol) in methylene chloride (1 L) at 0 °C is added dropwise boron trifluoride diethyl etherate (116 g, 0.82 mol). The resulting solution is stirred at room temperature for 18 h. The reaction mixture is washed with saturated Na_2CO_3 to pH 7. The organic layer is separated, dried (Na_2SO_4) and concentrated to give 180 g **DL2** (100%) as a thick oil. TLC (ethyl acetate:hexane 2:3) Rf 0.42. ^1H NMR ($CDCl_3$) δ 7.60-7.55 (m, 2H), 7.35-7.20 (m, 3H), 5.52 (s, 1H), 5.35-5.29 (m, 3H), 4.60-4.50 (m, 1H), 4.35-4.25 (m, 1H), 4.20-4.10 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H).

6.49.

Phenyl thio-a-D-mannopyranoside (DL3)

To a stirred solution of **DL2** (180 g, 0.41 mol) in anhydrous methanol (1 L) at 0 °C is added sodium methoxide (33 g, 0.61 mol). The reaction mixture is stirred at room temperature for 16 h. To the milky suspension is added Amberlite IR120 (plus) ion exchange resin until the pH of the suspension reaches 6. The mixture is filtered. The filtrate is concentrated and co-evaporated with dry toluene (5 x 50 mL). The residue is dissolved in a small amount of methanol. To the methanol solution is added ethyl acetate until white solid precipitated out. Solid is collected by filtration to give 63 g of **DL3** (56%). The filtrate is concentrated to give an oily form of **DL3** (45 g, 40%) whose TLC and ^1H NMR are identical with those of the solid. TLC (methanol:methylene chloride 1:4) Rf 0.63. ^1H NMR (D_2O) δ 7.44 (m, 2H), 7.27(m, 3H), 5.38 (d, 1H, J = 1.2 Hz), 4.15-4.00 (m, 2H), 3.80-3.50 (m, 4H).

6.50.

Phenyl 4,6-O-benzylidene-1-thio-α-D-mannopyranoside (DL4)

To a stirred solution of **DL3** (3.5 g, 12.8 mmol) and benzylidene dimethyl acetal (2.15 g, 14 mmol) in DMF (40 mL) is added toluenesulfonic acid (300 mg). The solution is stirred at room temperature for 16 h. Solvent is removed by evaporation. The residue is dissolved in ethyl acetate, washed with saturated $NaHCO_3$, then dried (Na_2SO_4). The solvent is evaporated to give 3 g (67%) of **DL4** as a solid. TLC (methanol:methylene chloride 1:9) Rf 0.51. ^1H NMR ($CDCl_3$) δ 7.52-7.46 (m, 4H), 7.38-7.30 (m, 6H), 5.60 (s, 1H), 5.58 (d, 1H, J = 0.9), 4.40-4.20 (m, 3H), 4.05 (m, 2H), 3.85 (t, 1H). Fab MS: 383 $(M+Na)^+$.

6.51.
Phenyl 2-O-benzyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside (DL5)

To a stirred solution of **DL4** (5.66 g, 16 mmol) and benzyl bromide (3.80 g, 22.4 mmol) in DMF (50 mL) at room temperature is added silver oxide (5.5 g). The suspension is stirred at room temperature for 48 h. The reaction mixture is filtered. Solvent is removed by evaporation. The residue is dissolved in ethyl acetate (50 mL), washed with water, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica (15% ethyl acetate in hexane) furnishes 3.6 g (50%) of **DL5** as a thick oil. TLC (ethyl acetate:hexane 1:4) Rf 0.3. ^1H NMR ($CDCl_3$) δ 7.60-7.20 (m, 15H), 5.58 (s, 2H), 4.70 (dd, 2H, J = 36.9 Hz, 11.7 Hz), 4.20-4.05 (m, 4H), 3.96 (t, 1H, J = 9.6 Hz), 3.84 (t, 1H, J = 10.2 Hz).

6.52.
Phenyl 3-O-allyl-2-O-benzyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside (DL6)

To a stirred solution of **DL5** (3.5 g, 7.7 mmol) in anhydrous DMF (50 mL) at 0 °C is added NaH (95%, 390 mg). The suspension is stirred for 30 min. Allyl

bromide (1.86 g, 15.5 mmol) is added. The mixture is stirred at room temperature for 18 h. Methanol is added until a clear solution is observed. Solvent is removed by evaporation. The residue is dissolved in ethyl acetate, washed with saturated NH_4Cl, dried (Na_2SO_4) and concentrated to give 3.6 g (95%) of DL6 as a thick oil. TLC (ethyl acetate:hexane 1:9) Rf 0.41. ^1H NMR (CD_3OD) δ 7.55-7.26 (m, 15H), 6.00-5.80 (m, 1H), 5.63 (s, 1H), 5.52 (d, 1H, J = 1.5 Hz), 5.30 (dm, 1H, J =17.4 Hz), 5.20 (dm, 1H, J = 10.5 Hz), 4.76 (s, 2H), 4.40-4.00 (m, 6H), 3.85 (d, 2H, J = 10.2 Hz). Fab MS: 513 $(M+Na)^+$.

6.53.
Phenyl 3-O-allyl-2,6-di-O-benzyl--1-thio-α-D-mannopyranoside (DL7)

To a stirred mixture of DL6 (3 g, 6.1 mmol), $NaBH_3CN$ (3.7 g, 17 mmol) and molecular sieves 3Å (500 mg) in anhydrous THF at 0 °C is added HCl ether solution (1M) until no air bubbles can be observed. The mixture is stirred at 0 °C for 3 h or until TLC indicates the absence of starting material. The reaction mixture is poured into ice water. The mixture is extracted with ethyl acetate (3 x 30 mL), dried and concentrated. The residue is purified by flash chromatography (20% ethyl acetate in hexane) to give 2.55 g (85%) of DL7 as a waxy solid. TLC (ethyl acetate:hexane 1:4) Rf 0.3. ^1H NMR ($CDCl_3$) δ 7.50-7.20 (m, 15H), 6.00-5.80 (m, 1H), 5.61 (d, 1H, J = 1.2 Hz), 5.35-5.20 (m, 2H), 4.80-4.50 (m, 4H), 4.30 (m, 1H), 4.15-3.90 (m, 4H), 3.80 (m, 2H), 3.60 (dd, 1H, J = 9.3 Hz, 3.0 Hz), 2.60 (bs, 1H). Fab MS: 515 $(M+Na)^+$.

6.54.
Phenyl 4-O-acetyl-3-O-allyl-2,6-di-O-benzyl--1-thio-α-D-mannopyranoside (DL8)

To a stirred solution of **DL7** (10 g, 20 mmol) and 4-N,N-dimethylpyridine (500 mg) in dry pyridine is added acetic anhydride (3.1 g, 30 mmol). The mixture is stirred at room temperature for 16 h. Solvent is removed by evaporation. The residue is dissolved in ethyl acetate, washed with cold aqueous HCl (1M), saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated to give 11 g (100%) of **DL8** as a thick oil. TLC (ethyl acetate:hexane 1:2) Rf 0.73. ^1H NMR ($CDCl_3$) δ 7.50-7.20 (m, 15H), 6.90-6.75 (m, 1H), 5.58 (d, 1H, J = 1.5 Hz), 5.40-5.20 (m, 3H), 4.70 (d, 2H, J = 5.7 Hz), 4.50 (d, 2H, J = 2.4 Hz), 4.15-3.90 (m, 4H), 3.75-3.60 (m, 3H), 2.02 (s, 3H).

6.55.
Phenyl 4-O-acetyl-3-O-allyl-2,6-di-O-benzyl-1-thio-α-D-mannopyranoside S-oxide (DL9)

To a stirred solution of **DL8** (11 g, 20 mmol) in ethyl acetate (100 mL) at -30 °C is added dropwise mCPBA (68.7%, 5.17g, 20 mmol) in ethyl acetate (20 mL). The solution is stirred at
-30 °C for 30 min until TLC indicates the absence of starting material. The cold solution is washed with concentrated Na_2CO_3. The organic layer is dried (Na_2SO_4) and concentrated to give 11.5 g (100%) of **DL9** as a thick oil. TLC (ethyl acetate:hexane 1:2) ^1H NMR ($CDCl_3$) δ 7.60-7.20 (m, 15H), 5.80 (m, 1H), 5.40-5.20 (m, 3H), 4.70-4.00 (m, 10H), 3.60 (m, 2H), 2.05 (s, 3H). Fab MS: 573 $(M+Na)^+$.

6.56.
Methoxycarbonylmethylenyl 4-O-acetyl-3-O-allyl-2,6-di-O-benzyl-α-D-mannopyranoside (DL10) and Methoxycarbonylmethylenyl 4-O-acetyl -3-O-allyl-2,6-di-O-benzyl-β-D-mannopyranoside (DL11)

To a stirred solution of **DL9** (10.6 g, 19.3 mmol) in dry toluene (200 mL) at -78 °C is added trifluoromethanesulfonic anhydride (5.4 g, 19.3 mmol).

After 30 min stirring, 2,6-di-t-butyl-4-methylpyridine in toluene (20 mL) is added. The mixture is stirred for 20 min. Methyl glycolate (1.8 g, 20 mmol) is added. The solution is stirred at -78 to -70 °C for 2 h. The reaction is quenched with saturated $NaHCO_3$ solution (100 mL), extracted with ethyl acetate (3 x 100 ml), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (10 → 25% ethyl acetate in hexane) to give 4 g (41%) of **DL10** and 2 g (20.5%) of **DL11** as thick oils. **DL10**: TLC (ethyl acetate:hexane 1:2) Rf 0.43. ^1H NMR ($CDCl_3$) δ 7.40-7.20 (m, 10H), 6.00-5.80 (m, 1H), 5.27 (dm, 1H, J = 17.1 Hz), 5.18 (dm, 1H, J = 10.5 Hz), 5.04 (d, 1H, J = 1.8 Hz, H-1β), 4.73 (dd, 2H, J = 24.6 Hz, 12.6 Hz), 4.61 (s, 2H), 4.22-3.75 (m, 10H), 3.72 (s, 3H, CO_2CH_3), 3.55 (m, 2H), 1.97 (s, 3H). Fab MS: 537 (M+Na)⁺. **DL11**: TLC (ethyl acetate:hexane 1:2) Rf 0.31. ^1H NMR ($CDCl_3$) δ 7.50-7.25 (m, 10H), 5.95-5.85 (m, 1H), 5.30-5.05 (m, 2H), 4.89 (dd, 2H, J = 27.3 Hz, 12.3 Hz), 4.52 (d, 1H, J = 3.0 Hz, H-1α), 4.38 (d, 1H, J = 6.0 Hz), 4.05-3.37 (m, 12H), 1.97 (s, 3H). Fab MS: 537 (M+Na)⁺.

6.57.
Methoxycarbonylmethylenyl 3-O-allyl-2,6-di-O-benzyl-α-D-mannopyranoside (DL12)

To a stirred solution of **DL10** (4.0 g, 7.78 mmol) in anhydrous methanol (150 mL) at room temperature is added sodium methoxide (420 mg, 7.78 mmol). The solution is stirred for 3 h. Amberlite IR-120 (plus) ion exchange resin is added until the pH of the solution reaches 7. The mixture is then filtered and concentrated. The residue is dissolved in ethyl acetate (50 mL), washed with H_2O, dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (30% ethyl acetate in hexane) to give 2.5 g (68%) of **DL12** as a thick oil. TLC (ethyl acetate:hexane 1:2) 0.25. ^1H NMR ($CDCl_3$) δ 7.36- 7.26

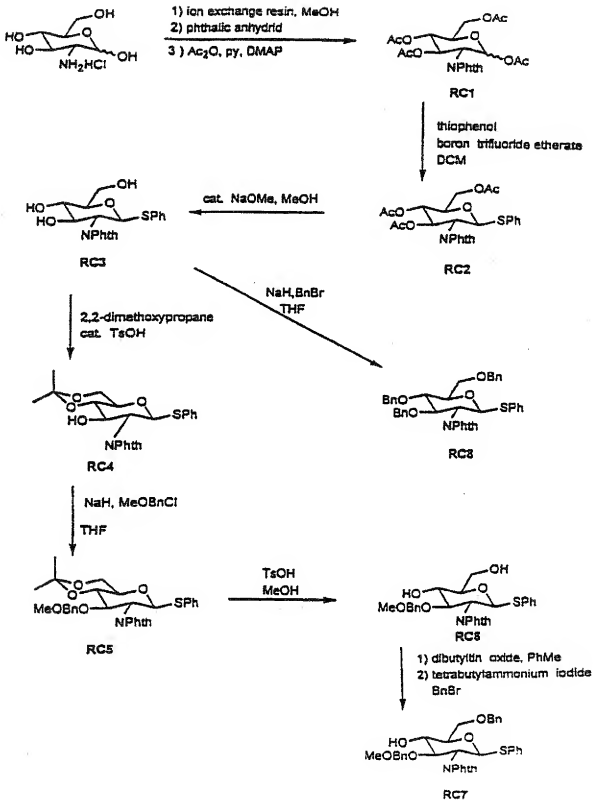
(m, 10H), 6.00-5.80 (m, 1H), 5.27 (dm, 1H, J = 17.1 Hz), 5.18 (dm, 1H, J = 10.5 Hz), 5.04 (d, 1H, J = 1.8 Hz), 4.69 (d, 1H, J = 3.6Hz), 4.60 (d, 1H, J = 4.2 Hz), 4.22-3.75 (m, 10H), 3.73 (s, 3H, $COCH_3$), 3.65 (dd, 1H, J = 9.6 Hz, 3.3 Hz). 2.58 (bs, 1H). Fab MS: 496 $(M+Na+H)^+$.

6.58.
Phenyl 2,3,4,6-tetra-O-pivaloyl-1-thio-α-D-glucoside S-oxide (DL121)

A stirred solution of D-glucose (20 g, 111 mmol), trimethyacetyl chloride (80 g, 666 mmol) and DMAP (400 mg) in pyridine (150 mL) is heated at 80 °C for 48 h. Solvent is removed by evaporation. The residue is dissolved in ethyl acetate (150 mL), washed with cold aqueous HCl (1M) to pH 2, washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue (70 g) and thiophenol (13 mL, 130 mmol) are dissolved in methylene chloride (200 mL). To the ice bath cooled solution is added dropwise $BF_3.Et_2O$ (34 g, 240 mmol). The mixture is stirred at room temperature for 16 h and neutralized with saturated $NaHCO_3$. The organic layer is dried (Na_2SO_4) and concentrated. The residue (10 g, 16.4 mmol) is dissolved in ethyl acetate (100 mL) and cooled to -30 °C. The mCPBA (4.1 g, 16.4 mmol) in ethyl acetate (30 mL) is added dropwise. The mixture is stirred at -30 °C for 30 min, washed with saturated Na_2CO_3 to pH 8, dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (20% ethyl acetate in hexane) to give 8 g of **DL121** as a solid. TLC (30% ethyl acetate in hexane) Rf 0.45. ^1H NMR ($CDCl_3$) δ 7.74 (m, 2H), 7.54 (m, 3H), 5.35 (t, 1H, J = 9.3Hz), 4.99 (dd, 2H, J = 10.2Hz, 9.0Hz), 4.87 (t, 1H, J = 9.9Hz), 4.54 (d, 1H, 10.2Hz), 4.15-3.95 (m, 2H), 3.76-3.71 (m, 1H), 1.22 (s, 9H), 1.90 (s, 27H).

6.59.
Methoxycarbonylmethylenyl 3-O-allyl-2,6-di-O-benzyl-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL13)

To a stirred solution of phenyl 2,3,4,6-tetra-O-pivaloyl-1-thio-α-D-glucoside S-oxide (**DL121**, 6.9 g, 11 mmol) and 2,6-di-tert-butyl-4-methylpyridine (2.25 g, 11 mmol) in ethyl acetate/hexane (1:1, 60 mL) at -70 °C is added trifluoromethanesulfonic anhydride (3.1 g, 11 mmol). The solution is stirred for 30 min. at -70 °C. **DL12** in ethyl acetate/hexane (1:1, 15 mL) is added. The solution is stirred at -65 °C for 2.5 h and quenched with saturated $NaHCO_3$ (30 mL). The organic layer is separated. The aqueous layer is extracted with ethyl acetate (3 x 30 ml). Theextracts are combined and dried (Na_2SO_4), concentrated and purified by flash chromatography (20% ethyl acetate in hexane) to give 5.0 g (93%) of **DL13** as a thick oil. TLC (ethyl acetate:hexane 1:2) Rf 0.50. ^1H NMR ($CDCl_3$) δ 7.40-7.30 (m, 10H), 5.95-5.80 (m, 1H), 5.32 - 4.69 (m, 11H), 4.37 (d, 1H, J = 12Hz), 4.25-3.58 (m, 17H), 3.35 (bs, 1H), 1.22-1.05 (m, 36H). Fab MS: 993 $(M+Na)^+$.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RC2
RC3
NaH,BnBr
THF
2,2-dimethoxypropane
cat. TsOH
RC4
RC8
NaH, MeOBnCl
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TsOH
MeOH
RC5
RC6
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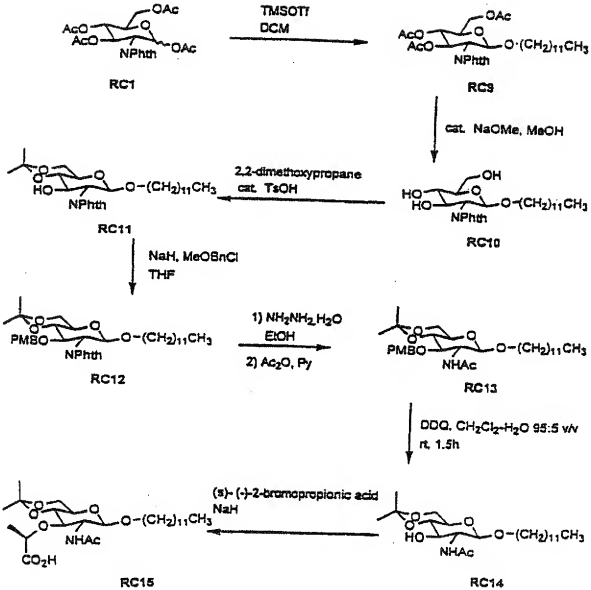
BnBr
RC7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1) NH2NH2.H2O
EtOH
2) Ac2O, Py
RC12
RC13
DDQ, CH2Cl2-H2O 95:5 v/v
rt, 1.5h
(s)- (-)-2-bromopropionic acid
NaH
RC15
RC14

6.60.
Hydroxycarbonylmethylenyl 3-O-allyl-2,6-di-O-benzyl-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL14)

A solution of **DL13** (5 g, 5.15 mmol) in aqueous KOH (0.1M)/dioxane (1:1, 60 mL) is stirred at room temperature for 24 h. Amberlite IR-120 (plus) ion exchange resin is added until the pH of the solution reaches 6. The mixture is filtered, concentrated and co-evaporated with dry toluene (3 x 20 mL) to give 4.7 g (95%) of **DL14** as a thick oil. TLC (methanol:methylene chloride 1:9) Rf 0.5. ^{1}H NMR ($CDCl_3$) δ 7.40-7.05 (m, 10H), 5.95-5.80 (m, 1H), 5.31-4.65 (m, 7H), 4.36 (d, 1H, J = 12Hz), 4.25-3.59 (m, 14H), 3.38 (bs, 1H), 1.18 (s, 3H), 1.17(s, 3H), 1.12 (s, 3H), 1.10 (s, 3H).

6.61.
Dodecylcarbamoylmethylenyl 3-O-allyl-2,6-di-O-benzyl-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL15)

A mixture of the compound **DL14** (2 g, 2.1 mmol), DCC (650 mg, 3.15 mmol), HOBT (425 mg, 3.15 mmol) and dodecylamine (583 mg, 3.15 mmol) in methylene chloride (30 mL) is stirred at room temperature for 16 h. The mixture is filtered and concentrated. The residue is purified by flash chromatography (30% ethyl acetate in hexane) to give 2 g (84%) of **DL15** as a thick oil. TLC (ethyl acetate:hexane 1:2) Rf 0.3. ^{1}H NMR ($CDCl_3$) δ 7.41-7.25 (m, 10H), 6.35 (t, 1H, J = 5.7 Hz, CONH), 5.95-5.80 (m, 1H), 5.30 (dd, 1H, J = 17.1, 1.8 Hz), 5.65 (dd, 1H, J = 10.5, 1.8 Hz), 5.05-4.85 (m, 4H), 4.79 (s, 1H), 4.75 (s, 1H), 4.40-3.90 (m, 14H), 3.75-3.13 (m, 4H), 1.27-1.09 (m, 56H), 0.87 (t, 3H, J = 7.0Hz). Fab MS: 1147 $(M+Na+H)^+$.

6.62.
Dodecylcarbamoylmethylenyl 2,6-di-O-benzyl-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL16)

To a solution of **DL15** (800 mg, 0.7 mmol) in methanol (25 mL) is added $PdCl_2$ (64 mg). The suspension is stirred at room temperature for 2.5 h or until TLC indicates the absence of starting material. The suspension is filtered. The filtrate is concentrated and purified with a short silica column (35% ethyl acetate in hexane) to give 720 mg (93%) of **DL16** as a thick oil. TLC (35% ethyl acetate in hexane) Rf 0.45. ^1H NMR ($CDCl_3$) δ 7.45-7.25 (m, 10H), 6.45(t, 1H, J = 5.7Hz), 5.10-4.70 (m, 6H), 4.40-3.10 (m, 16H), 1.40-1.05 (m, 56H), 0.87 (t, 3H, J = 7.0Hz). Fab MS: 1106 (M+Na)$^+$.

6.63.
Dodecylcarbamoylmethylenyl 2,6-di-O-benzyl-3-O-[1'(R)-(carboxy)ethyl]-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL17)

To a stirred solution of **DL16** (720 mg, 0.66 mmol) in dry THF at room temperature is added sodium hydride (95%, 66 mg, 2.6 mmol). The suspension is stirred at for 30 min. The reagent (s)-(-)-2-bromopropionic acid (150 mg, 1 mmol) is added. The mixture is stirred for 16 h. Methanol (2 mL) is added. The solution is evaporated. The residue is dissolved in ethyl acetate and washed with aqueous HCl (1M). The organic layer is dried (Na_2SO_4), concentrated and purified by flash chromatography (6-8% methanol in methylene chloride) to give 500 mg (65%) of **DL17** as a thick oil. TLC (10% methanol in methylene chloride) Rf 0.45. ^1H NMR ($CDCl_3$) δ 7.45-7.20 (m, 10H), 6.65 (t, 1H, J = 6.0Hz), 5.3-3.1 (m, 23H), 1.26-1.09 (m, 56H), 0.87 (t, 3H, J = 7.0Hz). Fab MS: 1205 (M+2Na+4).

6.64.
Dodecylcarbamoylmethylenyl 3-O-[1'(R)-(carboxy)ethyl]-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL18)

A suspension of **DL17** (500 mg, 0.5 mmol) and palladium on carbon (10%, 300 mg) in ethanol (10 mL) is subjected to hydrogenolysis at 50 psi for 48 h. The suspension is filtered and concentrated to give 400 mg (95%) of **DL18** as a thick oil. ^{1}H NMR (CD_3OD) δ 4.40-3.20 (m, 19H), 1.55-1.05 (m, 56H), 0.87 (t, 3H, J = 7.2Hz). Fab MS: 1020 (M+2Na-H).

6.65.
Dodecylcarbamoylmethylenyl 2,6-di-O-acetyl-3-O-[1'(R)-(carboxy)ethyl]-4-O-(2',3',4',6'-tetra-O-pivaloyl-1-β-D-glucosyl)-α-D-mannopyranoside (DL19)

A solution of **DL18** (340 mg, 0.35 mmol), acetic anhydride (107 mg, 3.15 mmol) and DMAP (10 mg) in dry pyridine is stirred at room temperature for 16 h. The solution is evaporated. The residue is dissolved in ethyl acetate (10 mL) and added to aqueous HCl (2M, 5 mL). The mixture is stirred for 2 h at room temperature. The organic layer is dried (Na_2SO_4), concentrated and purified by flash chromatography (2-10% methanol in methylene chloride) to give 55 mg (17%) of **DL19** as a thick oil. TLC (10% methanol in methylene chloride) 0.65. ^{1}H NMR (CD_3OD) δ 5.40-3.20 (m, 19H), 2.10 (m, 6H), 1.50-1.05 (m, 56H), 0.85 (t, 3H, J = 0.70Hz). Fab MS: 1105 (M+2Na).

6.66.
Phenyl 2-deoxy-2-N-phthalimido-1,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (RC1)

To a suspension of D-glucosamine hydrochloride (30 g, 138.9 mmol) in methanol (300 mL) is added Amberlite RA-400 (OH) ion exchange resin (99.2 mL, 138.9 mmol). The reaction mixture is stirred at room temperature for

1 h. The resin is removed by filtration, and the filtrate is treated with phthalic anhydride (20.6 g, 138.9 mmol). The reaction mixture is stirred at room temperature for 1.5 hr, and the solid intermediate is collected by filtration and dried. Phthalic anhydride (20.6 g, 138.9 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature overnight. More solid intermediate is obtained. The two portions of intermediate are combined (29.5 g, 64%). Next, 6 g (21.3 mmol) of the intermediate is dissolved in dichloromethane (70 mL). Pyridine (26 mL, 319.5 mmol), acetic anhydride (20 mL, 213 mmol) and DMAP (0.4 g, 15%) is added. After stirring at room temperature overnight, dichloromethane (100 mL) is added. The reaction solution is washed consecutively with 1N HCl (2 x 100 mL), saturated aqueous sodium bicarbonate (2 x 100 mL), water (2 x 100 mL) and brine (2 x 100 mL), dried (Na_2SO_4) and concentrated. The crude product (Qy) is used for the next step without further purification. TLC (EtOAc-Hexane 1:1) Rf 0.35. ^1H NMR ($CDCl_3$) δ 7.85-7.72 (m, 4H), 6.55 (dd, 1H, J=9.3Hz), 6.27 (d, 1H, J=3.3Hz), 5.15 (t, 1H, J=9.3Hz), 4.71 (dd, 1H, J=3.3Hz), 4.40-4.28 (m, 2H), 4.12 (m, 1H), 2.21 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.59, 169.71, 169.45, 169.24, 167.37, 134.40, 131.17, 123.67, 90.52, 70.19, 69.48, 67.04, 61.57, 52.83, 20.87, 20.63, 20.55.

6.67.
Phenyl 2-deoxy-2-N-phthalimido-1-thio-3,4,6-tri-O-acetyl-β-D-glucopyranoside (RC2)

To a cooled (0 °C) solution of RC1 (32 g, 67 mmol) in anhydrous dichloromethane (200 mL) is added thiophenol (7.6 mL, 73.7 mmol) followed by boron trifluoride etherate (16.5 mL, 134 mmol). The reaction mixture is allowed to warm up to room temperature and is stirred at 50 °C overnight. Dichloromethane (100

mL) is added. The reaction solution is washed consecutively with saturated aqueous sodium bicarbonate (2 x 200 mL), water (2 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4) and concentrated. The resulting product **RC2** (Qy) is used for the next step without further purification. TLC (EtOAc-Hexane 1:1) Rf 0.45. ^1H NMR ($CDCl_3$) δ 7.90-7.26 (m, 4H), 7.43-7.26 (m, 5H), 5.80 (t, 1H, J=9.3Hz), 5.71 (d, 1H, J=10.5Hz), 5.14 (t, 1H, J=9.3Hz), 4.35 (t, 1H, J=9.3Hz), 4.30-4.18 (m, 2H), 3.80 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.84 (s, 3H).

6.68.
Phenyl 2-deoxy-2-N-phthalimido-1-thio-β-D-glucopyranoside (RC3)

To a solution of **RC2** (34.0 g, 64.5 mmol) in methanol (200 mL) is added sodium methoxide (3.5 g, 64.8 mmol). The reaction mixture is stirred at room temperature overnight. Amberlite IR-120 plus (H) ion-exchange resin (50 mL, 95 mmol) is added. The mixture is stirred for 1h. The resin is removed by filtration and the filtrate is dried ($MgSO_4$) and concentrated. The resulting product **RC3** (Qy) is used in the next step without further purification. TLC (EtOAc-Hexane 7:3) Rf 0.42. ^1H NMR ($CDCl_3$) δ 7.84-7.22 (m, 9H), 5.64 (d, 1H, J=10.2Hz), 4.35 (t, 1H, J=8.7Hz), 4.20 (t, 1H, J=10.2Hz), 3.90 (m, 2H), 3.67 (t, 1H, J=8.7Hz), 3.57 (m, 1H).

6.69
Phenyl 2-deoxy-4,6-isopropylidine-2-N-phthalimido-1-thio-β-D-glucopyranoside (RC4)

To a solution of **RC3** (54.0 g, 134.6 mmol) in 2,2-dimethoxypropane (200 mL) is added *p*-toluenesulfonic acid (2.6 g, 13.46 mmol). The reaction mixture is stirred at room temperature overnight. Ethyl acetate (200 mL) is added. The reaction mixture is washed with saturated aqueous sodium bicarbonate (2 x 300 mL),

water (2 x 300 mL) and brine (2 x 300 mL), dried (Na_2SO_4) and concentrated. The resulting product RC4 (Qy) is used in the next step without further purification. TLC (EtOAc:Hexane 1:1) Rf 0.6. ^1H NMR ($CDCl_3$) δ 7.89-7.22 (m, 9H), 5.65 (d, 1H, J=10.5Hz), 4.47 (m, 1H), 4.28 (t, 1H, J=10.2Hz), 3.99 (q, 1H, J=5.4Hz), 3.82 (t, 1H, J=10.5Hz), 3.63 (t, 1H, J=9.3Hz), 3.53 (m, 1H), 2.34 (d, 1H, J=3Hz), 1.52 (s, 3H), 1.42 (s, 3H).

6.70.
Phenyl 2-deoxy-4,6-isopropylidine-3-O-*p*-methoxybenzyl-2-N-phthalimido-1-thio-β-D-glucopyranoside (RC5)

A solution of RC4 (60 g, 136 mmol) in tetrahydrofuran (200 mL) is added in a dropwise manner to a suspension of sodium hydride (6.87 g, 272 mmol)/tetrahydrofuran (30 mL). *p*-Methoxybenzyl chloride (27.66 mL, 204 mmol) is added. The reaction mixture is stirred at 65 °C for 24 h. The reaction is quenched with 2N HCl (200 mL) and ethyl acetate (300 mL) is then added. The organic layer is separated and washed with water (2 x 300 mL) and brine (2 x 300 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7, 2:3, 1:1) to furnish RC5 (35 g, 63%) and RC4 (16.2 g) as viscous liquids. TLC (EtOAc-Hexane 3:7) Rf 0.4, TLC (EtOAc-Hexane 1:1) Rf 0.5. ^1H NMR ($CDCl_3$) δ 7.80-7.13 (m, 9H), 6.85 (d, 2H, J=9Hz), 6.32 (d, 2H, J=9Hz), 5.55 (d, 1H, J=10.5Hz), 4.60 (d, 1H, J=12Hz), 4.34 (d, 1H, J=12Hz), 4.18 (m, 2H), 3.93 (q, 1H, J=5.4Hz), 3.77 (m, 2H), 3.53 (s, 3H), 3.49 (m, 1H), 1.48 (s, 3H), 1.41 (s, 3H).

6.71.
Phenyl 2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-1-thio-β-D-glucopyranoside (RC6)

To a solution of RC5 (3.6 g, 6.42 mmol) in methanol (36 mL) is added toluenesulfonic acid (0.12 g, 0.642 mmol). The reaction mixture is stirred at room temperature for 4.5 h. Amberlite RA-400 (OH) ion exchange resin (4.6 mL, 6.44 mmol) is added, and the mixture is stirred for 1 h. The resin is removed by filtration, and the filtrate is dried (Na_2SO_4) and concentrated. The resulting product RC6 (Qy) is used for the next step without further purification. TLC (EtOAc-Hexane 7:3) Rf 0.2. ^1H NMR ($CDCl_3$) δ 7.84-7.22 (m, 9H), 6.98 (d, 2H, J=8.7Hz), 6.51 (d, 2H, J=8.7Hz), 5.60 (d, 1H, J=9.6Hz), 4.58 (d, 1H, J=12Hz), 4.55 (d, 1H, J=12Hz), 4.24 (m, 2H), 3.99-3.67 (m, 3H), 3.64 (s, 3H), 3.57 (m, 1H).

6.72.
Phenyl 6-O-benzyl-2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-1-thio-β-D-glucopyranoside (RC7)

A solution of RC6 (7.39 g, 14.2 mmol) in toluene (100 mL) is heated under reflux for 1 h. Dibutyltin oxide (3.45 g, 14.2 mmol) is added. The reaction mixture is heated under reflux overnight. Tetrabutylammonium iodide (5.24 g, 14.2 mmol) and benzyl bromide (2.2 mL, 18.5 mmol) are added to the reaction mixture and stirred at 80 °C for 32 h. Ethyl acetate (150 mL) is added. The reaction mixture is washed with water (2 x 150 mL) and brine (2 x 150 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7 to 3:2) to furnish RC7 (6 g, 69%) as a viscous liquid. TLC (EtOAc-Hexane 1:1) Rf 0.45. ^1H NMR ($CDCl_3$) δ 7.84-7.18 (m, 9H), 6.95 (d, 2H, J=9Hz), 6.44 (d, 2H, J=9Hz), 5.56 (d, 1H, J=10.2Hz), 4.64 (d, 1H, J=12.3Hz), 4.60 (ABq, 2H), 4.55 (d, 1H, J=12.3Hz), 4.22 (m, 2H), 3.80 (m, 3H), 3.71 (q, 1H, J=5.1Hz), 3.62 (s, 3H), 2.85 (d, 1H, J=2.7Hz). Fab MS: 635 $(M+H+Na)^+$.

6.73.
Phenyl 2-deoxy-2-N-phthalimido-1-thio-3,4,6-tri-O-benzyl-β-D-glucopyranoside (RC8)

A solution of RC3 (22.5 g, 56.1 mmol) in tetrahydrofuran (150 mL) is dropped into a suspension of sodium hydride (8.5 g, 336.6 mmol)/tetrahydrofuran (20 mL). Benzyl bromide (24 mL, 202 mmol) is added. The reaction mixture is stirred at 65 °C overnight. The reaction is quenched with 2N HCl (100 mL) and ethyl acetate (200 mL) is added. The organic layer is washed with water (2 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 1:9, 1:4, 3:7) to furnish RC8 (17.42 g, 46%) as a viscous liquid. TLC (EtOAc-Hexane 3:7) Rf 0.55. ^1H NMR ($CDCl_3$) δ 7.82-6.83 (m, 24H), 5.53 (d, 1H, J=10.5Hz), 4.85-4.54 (m, 5H), 4.38 (m, 2H), 4.25 (m, 1H), 3.85-3.68 (m, 4H). Fab MS: 694 $(M+Na)^+$.

6.74.
Dodecyl 2-deoxy-2-N-phthalimido-3,4,6-tri-O-acetyl-β-D-glucopyranoside (RC9)

To a stirred mixture of RC1 (9.85 g, 20.6 mmol), 1-dodecanol (3.8 g, 20.6 mmol) and molecular sieves in dichloromethane (50 mL) is added trimethylsilyl trifluoromethanesulfonate (10 mL, 51.5 mmol). The reaction mixture is stirred at room temperature for 3 h. The reaction mixture is poured into saturated aqueous sodium bicarbonate (100 mL), and ethyl acetate (100 mL) is added. The organic layer is separated and washed with water (2 x 150 mL) and brine (2 x 100 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7) to furnish RC9 (7.83 g, 63%) as a white powder. TLC (EtOAc-Hexane 3:7) Rf 0.55. ^1H NMR ($CDCl_3$) δ 7.88-7.72 (m, 4H), 5.79 (dd, 1H, J=9.3Hz), 5.35 (d, 1H, J=8.7Hz), 5.17 (t, 1H, J=10.2Hz), 4.31 (m, 2H), 4.16 (dd, 1H,

J=2.4Hz), 3.84 (m, 2H) 3.41 (m, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.87 (s, 3H), 1.25-1.00 (m, 20H), 0.88 (t, 3H, J=7.2Hz). Fab MS: 626 $(M+Na)^+$.

6.75.
Dodecyl 2-deoxy-2-N-phthalimido-β-D-glucopyranoside (RC10)

To a solution of RC9 (10.35 g, 17.1 mmol) in methanol (50 mL) is added sodium methoxide (0.93 g, 17.1 mmol). The reaction mixture is stirred at room temperature for 3 h. Amberlite IR-120 plus (H) ion-exchange resin (12 mL, 2.04 mmol) is added. The reaction mixture is stirred for 1 h. The resin is removed by filtration, and the filtrate is dried (Ma_2SO_4) and concentrated. The resulting product RC10 (Qy) is used in the next step without further purification. TLC (EtOAc) Rf 0.60. ^1H NMR (CD_3OD) δ 7.88-7.80 (m, 4H), 5.15 (d, 1H, J=8.4Hz), 4.25 (dd, 1H, J=8.4Hz), 4.00-3.82 (m, 3H), 3.75 (dd, 1H, J=5.4Hz), 3.42 (m, 3H), 1.37-1.00 (m, 20H), 0.88 (t, 3H, J=6.9Hz). Fab MS: 500 $(M+Na)^+$.

6.76.
Dodecyl 2-deoxy-4,6-isopropylidine-2-N-phthalimido-β-D-glucopyranoside (RC11)

To a solution of RC10 (5.7 g, 11.95 mmol) in 2,2-dimethoxypropane (50 mL) is added *p*-toluenesulfonic acid (285 mg, 15%). The reaction mixture is stirred at room temperature for 5 h. Ethyl acetate (100 mL) is added. The organic layer is separated and washed with saturated aqueous sodium bicarbonate (2 x 150 mL), water (2 x 150 mL) and brine (2 x 150 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7 to 3:7) to furnish RC11 (2.02 g, 39%) as a viscous liquid. TLC (EtOAc:Hexane 1:1) Rf 0.6. ^1H NMR ($CDCl_3$) δ 7.85-7.69 (m, 4H), 5.19 (d, 1H, J=8.4Hz), 4.42 (dd, 1H, J=8.7Hz),

4.16 (dd, 1H, J=8.7Hz), 3.95 (q, 1H, J=5.4Hz), 3.80 (m, 2H), 3.60 (t, 1H, J=6.9Hz), 3.45-3.62 (m, 2H), 1.50 (s, 3H), 1.41 (s, 3H), 1.30-0.99 (m, 20H), 0.86 (t, 3H, J=6.9Hz). Fab MS: 517 (M+Na)$^+$.

6.77.
Dodecyl 2-deoxy-4,6-isopropylidine-3-O-p-methoxybenzyl-2-N-phthalimido-β-D-glucopyranoside (RC12)

A solution of **RC11** (2.0 g, 3.87 mmol) in tetrahydrofuran (12 mL) is added dropwise to a suspension of sodium hydride (147 mg, 5.81 mmol)/tetrahydrofuran (3 mL). *p*-Methoxybenzyl chloride (0.79 mL, 5.81 mmol) is added. The reaction mixture is stirred at 65 °C for 24 h. The reaction is quenched with 2N HCl (20 mL) and ethyl acetate (50 mL) is added. The organic layer is separated and washed with water (2 x 100 mL) and brine (2 x 100 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7) to furnish **RC12** (1.28 g, 63%) as a viscous liquid. TLC (EtOAc-Hexane 3:7) Rf 0.6. ^{1}H NMR ($CDCl_3$) δ 7.86-7.60 (m, 4H), 6.85 (d, 2H, J=9Hz), 6.40 (d, 2H, J=9Hz), 5.14 (d, 1H, J=8.4Hz), 4.61 (d, 1H, J=12Hz), 4.38 (d, 1H, J=12Hz), 4.14 (m, 2H), 3.97 (q, 1H, J=5.4Hz), 3.80 (m, 3H), 3.62 (s, 3H), 3.49-3.30 (m, 2H), 1.54 (s, 3H), 1.47 (s, 3H), 1.3-0.96 (m, 20H), 0.88 (t, 3H, J=6.9Hz). Fab MS: 660 (M+Na)$^+$.

6.78.
Dodecyl 2-acetamido-2-deoxy-4,6-isopropylidine-3-O-p-methoxybenzyl-β-D-glucopyranoside (RC13)

A solution of **RC13** (623 mg, 1 mmol) and hydrazine hydrate (1 mL, 20 mmol) in 95% EtOH (10 mL) is heated under reflux for 6.5 h. White precipitate is filtered off, and the filtrate is concentrated. The residue is dissolved in pyridine (10 mL) and acetic anhydride (1.4 mL, 15 mmol). The reaction mixture is stirred at room

temperature for 2 h. Methanol (0.8 mL) is added, and the reaction mixture is stirred at room temperature for 1 h. Ethyl acetate is added (100 mL) and the reaction mixture is washed with saturated aqueous sodium bicarbonate (2 x 50 mL), water (2 x 100 mL) and brine (2 x 50 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc-Hexane 3:17 to 3:7) to furnish **RC13** (320 mg, 60%) as a viscous liquid. TLC (EtOAc-Hexane 3:7) Rf 0.6, TLC (EtOAc-Hexane 1:1) Rf 0.25. ^1H NMR ($CDCl_3$) δ 7.22 (d, 2H, J=8.7Hz), 6.86 (d, 2H, J=8.7Hz), 5.42 (d, 1H, J=8.7Hz), 4.91 (d, 1H, J=8.1Hz), 4.75 (d, 1H, J=11.1Hz), 4.53 (d, 1H, J=11.1Hz), 4.08 (t, 1H, J=9.6Hz), 3.92 (q, 1H, J=5.4Hz), 3.80 (s, 3H), 3.78 (m, 1H), 3.67 (t, 1H, J=9.6Hz), 3.46-3.14 (m, 3H), 1.89 (s,3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.24 (br s, 20H), 0.87 (t, 3H, J=6.9Hz). Fab MS: 572 $(M+Na)^+$.

6.79.
Dodecyl 2-acetamido-2-deoxy-3,4-isopropylidine-β-D-glucopyranoside (RC14)

To a solution of **RC13** (300 mg, 0.56 mmol), in dichloromethane (10 mL) is added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (165 mg, 0.73 mmol). The reaction mixture is stirred at room temperature for 1.5 h. The reaction mixture is poured into a 10% solution of sodium bisulfite (30 mL) and dichloromethane (50 mL) is added. The organic layer is separated, washed with water (2 x 50 mL) and brine (2 x 30 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc-MeOH, 1:0 to 9:1) to furnish **RC14** (180 mg, 75%) as a viscous liquid. TLC (EtOAc) Rf 0.15. ^1H NMR ($CDCl_3$) δ 6.44 (d, 1H, J=6.9Hz), 4.57 (d, 1H, J=8.4Hz), 3.80 (m, 4H), 3.50 (m, 2H), 3.25 (m, 1H), 2.00 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.22 (br s, 20H), 0.85 (t, 3H, J=6.6Hz). Fab MS: 452 $(M+Na)^+$.

6.80.
Dodecyl 2-acetamido-3-O-(1-carboxy)ethyl-2-deoxy-4,6-isopropylidine-β-D-glucopyranoside (RC15)

To a solution of **RC14** (180 mg, 0.42 mmol) in anhydrous tetarhydrofuran (4 mL) is added sodium hydride (42.4 mg, 1.68 mmol). The reaction mixture is stirred at room temperature for 30 min. (S)-(-)-2-Bromopropionic acid (0.057 mL, 0.63 mmol) is added and stirred at room temperature for 24 h. The reaction mixture is poured into HCl (2 N, 20 mL) and ethyl acetate (50 mL) is added. The organic layer is separated, washed with water (2 x 50 mL) and brine (2 x 30 mL) dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc-MeOH 1:0 to 9:1) to furnish **RC15** (140 mg, 67%) as a viscous liquid. TLC (EtOAc) Rf 0.15. ^1H NMR ($CDCl_3$) δ 4.58 (d, 1H, J=8.1Hz), 4.37 (t, 1H, J=8.7Hz), 3.92-3.74 (m, 4H), 3.59 (m, 2H), 3.45 (q, 1H, J=13.2Hz), 3.27 (m, 1H), 2.03 (s, 3H), 1.80 (d, 3H, J=6.9Hz), 1.49 (s, 3H), 1.41 (s, 3H), 1.23 (br s, 20H), 0.86 (t, 3H, J=6.9Hz). Fab MS: 546 $(M-H+Na+Na)^+$.

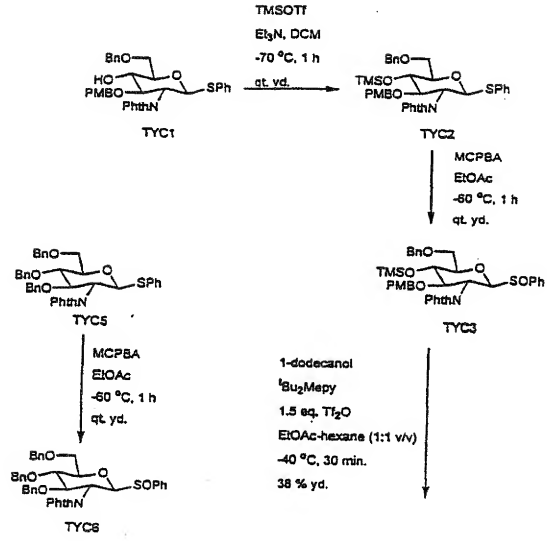
6.81.
Phenyl 6-O-Benzyl-2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-1-thio-4-O-trimethylsilyl-β-D-glucopyranoside (TYC2)

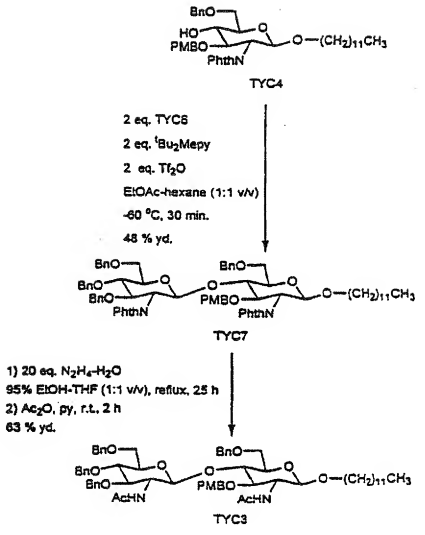
To a cooled (-70 °C) solution of **TYC1** (5.94 g, 9.72 mmol) and triethylamine (2.7 mL, 19.4 mmol) in dichloromethane (50 mL) is added trimethylsilyl trifluoromethanesulfonate (2.3 mL, 11.9 mmol). The reaction mixture is stirred for 1 h at 70 °C. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (50 mL). The organic layer is separated and the aqueous layer is extracted with dichloromethane (50 mL). The combined organic layers is washed with water (100 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The crude

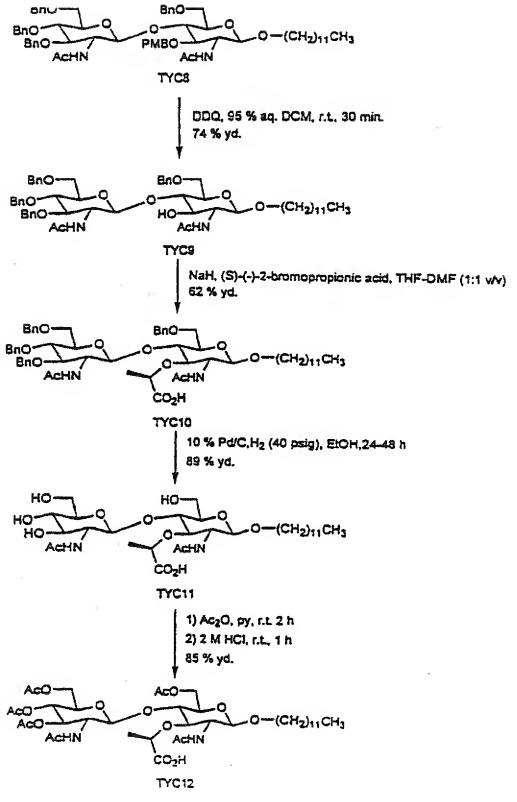
product (quantitative yield or Qy) is used in the next step without further purification. TLC (EtOAc:Hexane 1:1) Rf 0.66. ^{1}H NMR ($CDCl_3$): δ 7.80-7.55 (m, 4H), 7.45-7.25 (m, 7H), 7.25-7.10 (m, 3H), 6.90 (d, 2H, J=8.7Hz), 6.36 (d, 2H, J=8.7Hz), 5.54 (d, 1H J=10.2Hz), 4.71 (d, 1H, J=12Hz), 4.61 (ABq, 2H), 4.27 (d, 1H, J=12Hz), 4.22-4.17 (m, 2H), 3.85-3.60 (m, 4H), 3.56 (s, 3H), 0.16 (s, 9H).

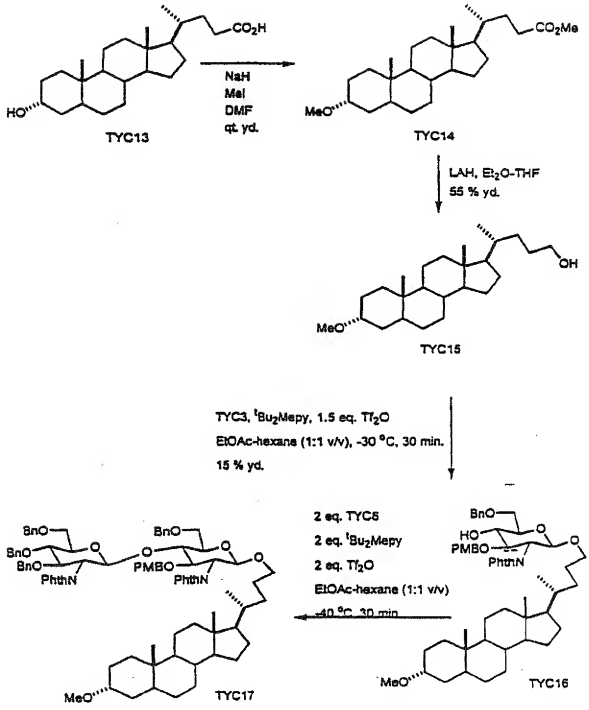
6 . 8 2 Phenyl 6-O-Benzyl-2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-1-sulfinyl-4-O-trimethylsilyl-β-D-glucopyranoside (TYC3)

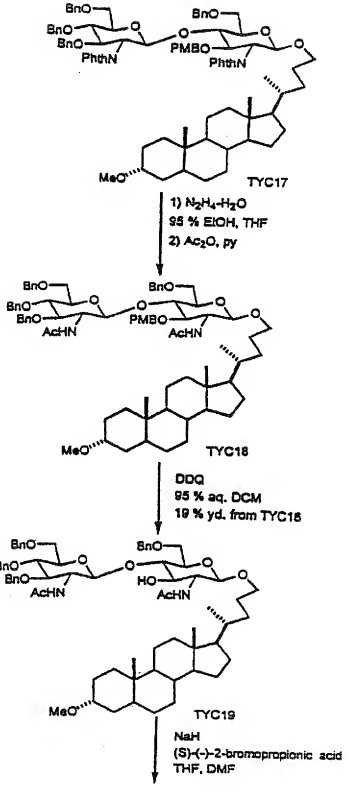
To a cooled (-60 °C) solution of TYC2 (0.54 g, 0.79 mmol) in ethyl acetate (5.0 mL) is added a solution of 3-chloroperoxybenzoic acid (68.7%, 0.20 g, 0.79 mmol) in ethyl acetate (3.0 mL). The reaction mixture is allowed to warm up to -30 °C in 1 h. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (20 mL), and ethyl acetate (20 mL) is added. The organic layer is separated and washed with water (20 mL) and saturated brine (20 mL), then dried (Na_2SO_4) and concentrated. The crude product (Qy) is used in the next step without further purification. TLC (EtOAc:Hexane 1:1) Rf 0.48.

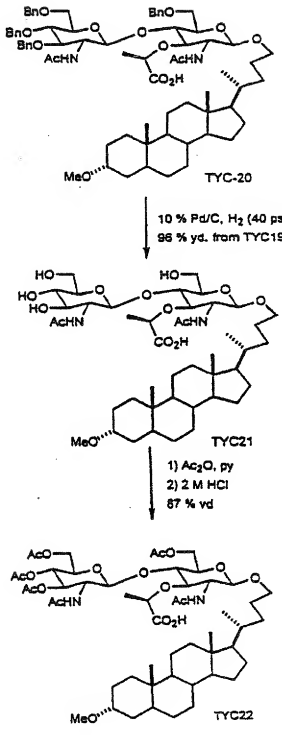

TMSOTf
Et3N, DCM
-70 °C, 1 h
qt. yd.
BnO
HO
PMBO
PhthN
SPh
TYC1
TMSO
TYC2
MCPBA
EtOAc
-60 °C, 1 h
qt. yd.
BnO
TMSO
PMBO
PhthN
SOPh
TYC3
1-dodecanol
tBu2Mepy
1.5 eq. Tf2O
EtOAc-hexane (1:1 v/v)
-40 °C, 30 min.
38 % yd.
BnO
BnO
BnO
PhthN
SPh
TYC5
MCPBA
EtOAc
-60 °C, 1 h
qt. yd.
SOPh
TYC6


BnO
HO
PMBO
PhthN
O—(CH2)11CH3
TYC4
2 eq. TYC6
2 eq. tBu2Mepy
2 eq. Tf2O
EtOAc-hexane (1:1 v/v)
-60 °C, 30 min.
48 % yd.
BnO
BnO
BnO
PhthN
PMBO
PhthN
TYC7
1) 20 eq. N2H4-H2O
95% EtOH-THF (1:1 v/v), reflux, 25 h
2) Ac2O, py, r.t., 2 h
63 % yd.
AcHN
AcHN
TYC3


TYC8
DDQ, 95 % aq. DCM, r.t., 30 min.
74 % yd.
TYC9
NaH, (S)-(-)-2-bromopropionic acid, THF-DMF (1:1 v/v)
62 % yd.
TYC10
10 % Pd/C,H2 (40 psig), EtOH,24-48 h
89 % yd.
TYC11
1) Ac2O, py, r.t. 2 h
2) 2 M HCl, r.t., 1 h
85 % yd.
TYC12


CO2H
NaH
MeI
DMF
qt. yd.
HO
TYC13
CO2Me
MeO
TYC14
LAH, Et2O-THF
55 % yd.
OH
MeO
TYC15
TYC3, tBu2Mepy, 1.5 eq. Tf2O
EtOAc-hexane (1:1 v/v), -30 °C, 30 min.
15 % yd.
2 eq. TYC5
2 eq. tBu2Mepy
2 eq. Tf2O
EtOAc-hexane (1:1 v/v)
-40 °C, 30 min
BnO
PMBO
PhthN
MeO
TYC17
HO
TYC16


BnO
BnO
BnO
PhthN
PMBO
PhthN
MeO
TYC17
1) N_2H_4-H_2O
95 % EtOH, THF
2) Ac_2O, py
AcHN
AcHN
TYC18
DDQ
95 % aq. DCM
19 % yd. from TYC18
HO
TYC19
NaH
(S)-(-)-2-bromopropionic acid
THF, DMF


BnO
BnO
BnO
AcHN
BnO
AcHN
CO_2H
MeO
TYC-20
10 % Pd/C, H_2 (40 psig), EtOH
96 % yd. from TYC19
HO
HO
HO
AcHN
HO
AcHN
CO_2H
MeO
TYC21
1) Ac_2O, py
2) 2 M HCl
87 % yd
AcO
AcO
AcO
AcHN
AcO
AcHN
CO_2H
MeO
TYC22

**6 . 8 3 .
Dodecyl6-O-Benzyl-2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-β-D-glucopyranoside (TYC4)**

A solution of **TYC3** (2.15 g, 3.07 mmol), 2,6-di-tert-butyl-4-methylpyridine (0.63 g, 3.07 mmol) and 1-dodecanol (0.57 g, 3.07 mmol) in EtOAc-hexane (1:1 v/v, 30 mL) is dropped into a cooling bath (-40 °C) followed quickly by the addition of trifluoromethanesulfonic anhydride (0.56 mL, 4.65 mmol). The reaction mixture is stirred for 30 min. at -40 °C. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (30 mL). The organic layer is separated, and the aqueous layer is extracted with ethyl acetate (30 mL). The combined organic layers is washed with water (60 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7 to 10:0) to furnish **TYC4** (0.75 g, 38%) as a viscous liquid. TLC (EtOAc-Hexane 3:7) Rf 0.25. TLC (EtOAc-Hexane 1:1) Rf 0.65. ^1H NMR ($CDCl_3$): δ 7.80 (s, br, 1H), 7.67 (s, br ,1H), 7.40-7.25 (m, 5H), 6.97 (d, 2H, J=8.7Hz), 6.46 (d, 2H, J=8.7Hz), 5.13 (d, 1H, J=8.4Hz), 4.67 (d, 1H, J=12.0 Hz), 4.62 (ABq, 2H), 4.47 (d, 1H, J=12.0Hz), 4.20 (dd, 1H, J=8.1,10.8Hz), 4.10 (dd, 1H, J=8.1,10.8Hz), 3.85-3.70 (m, 4H), 3.70-3.60 (m, 4H), 3.62 (s, 3H), 3.40-3.30 (m, 1H), 2.94 (d, 1H, J=2.4 Hz), 1.45-0.80 (m, 20 H), 0.88 (t, 3H, J=6.8Hz). ^{13}C NMR ($CDCl_3$): δ 158.79, 133.64, 129.50, 128.46, 127.82, 127.76, 113.43, 98.28, 78.39, 74.50, 73.87, 73.74, 73.54, 70.78, 69.63, 55.44, 31.87, 29.56, 29.54, 29.40, 29.30, 29.21, 29.12, 25.76, 22.65, 14.09. Fab MS: 710 $(M+Na)^+$.

**6 . 8 4 .
Phenyl 2-Deoxy-2-N-phthalimido-1-sulfinyl-3,4,6-tri-O-benzyl-β-D-glycopyranoside (TYC6)**

To a cooled (-60 °C) solution of **TYC5** (0.28 g, 0.42 mmol) in ethyl acetate (3.0 mL) is added a solution of 3-chloroperoxybenzoic acid (68.7%, 0.11 g, 0.43 mmol) in ethyl acetate (1.0 mL). The reaction mixture is allowed to warm up to -30 °C in 1 h. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (20 mL), and ethyl acetate (30 mL) is added. The organic layer is separated and washed with water (20 mL) and saturated brine (20 mL), then dried (Na_2SO_4) and concentrated. The crude product (Qy) is used in the next step without further purification. TLC (EtOAc:Hexane 1:1) Rf 0.42.

**6 . 8 5 .
Dodecyl (2-Deoxy-2-N-phthalimido-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-deoxy-6-O-benzyl-3-O-p-methoxybenzyl-2-N-phthalimido-β-D-glucopyranoside (TYC7)**

To a cooled (-60 °C) solution of **TYC4** (0.23 g, 0.33 mmol), **TYC6** (0.53 g, 0.77 mmol) and 2,6-di-tert-butyl-4-methylpyridine (0.16 g, 0.78 mmol) in EtOAc-hexane (1:1 v/v, 6 mL) is added trifluoromethanesulfonic anhydride (0.093 mL, 0.77 mmol). The reaction mixture is stirred for 30 min. at -60 °C. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (20 mL) and ethyl acetate (30 mL) is added. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (30 mL). The combined organic layers is washed with water (60 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 1:9 to 5:5) to furnish **TYC7** (0.19 g, 48%) as a viscous liquid. TLC (EtOAc-Hexane 3:7) Rf 0.19. TLC (EtOAc-Hexane 1:1) Rf 0.76. ^1H NMR ($CDCl_3$): δ 7.90-7.50 (m, 8H) 7.40-7.10 (m, 20H), 7.00-6.80 (m, 8H), 6.28 (d, 2H, J=8.4 Hz), 5.29 (d, 1H J=7.8Hz), 4.92 (d, 1H, J=8.1Hz), 4.85-4.75 (m, 3H), 4.70-4.30 (m, 10H), 4.30-4.00 (m, 4H), 3.95-3.15 (m,

12H), 3.57 (s, 3H), 1.20-0.80 (m, 25H), 0.87 (t, 3H, J=7.2Hz). ^{13}C NMR ($CDCl_3$): δ 158.31, 138.36, 138.28, 138.10, 138.07, 133.35, 131.67, 130.99, 129.65, 128.36, 128.32, 128.13, 127.98, 127.84, 127.65, 127.52, 127.21, 113.05, 98.06, 98.96, 79.60, 79.00, 76.49, 75.87, 75.03, 74.79, 74.72, 74.54, 73.84, 73.17, 72.57, 69.28, 68.23, 67.97, 56.71, 55.72, 54.7131.84, 29.53, 29.37, 29.27, 29.14, 29.09, 25.71, 22.62, 14.07. Fab MS: 1271 (M+Na)$^+$.

Dodecyl (2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-2-deoxy-3-O-p-methoxybenzyl-β-D-glucopyranoside (TYC8)

A solution of TYC7 (1.57 g, 1.26 mmol) and hydrazine hydrate (1.26 mL, 26.0 mmol) in 95% EtOH-THF (1:1 v/v, 26 mL) is heated under reflux for 24 h. White precipitate is filtered off and the filtrate is concentrated. The residue is dissolved in pyridine (12 mL), and acetic anhydride (1.2 mL, 12.7 mmol) is added. The reaction mixture is stirred for 2 h at room temperature. Methanol (2 mL, 49.4 mmol) is added. The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (50 mL), and ethyl acetate (100 mL) is added. The organic layer is separated, washed with water (100 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:DCM 5:5 to 7:3) to furnish TYC8 (0.85 g, 63%) as a viscous liquid. TLC (EtOAc:DCM 3:7) Rf 0.47. ^1H NMR ($CDCl_3$): δ 7.40-7.15 (m, 22H), 6.78 (d, 2H, J=8.7 Hz), 6.37 (d, 1H, J=8.7Hz), 4.92 (d, 1H, J=8.4Hz), 4.82 (d, 1H, J=6.6Hz), 4.78 (d, 1H, J=5.4Hz), 4.70-4.40 (m, 11H), 4.33 (d, 1H, J=8.1Hz), 4.10-3.90 (m, 2H), 3.90-3.60 (m, 11H), 3.75 (s, 3H), 3.49 (dd, 1H, J=8.4,10.2Hz), 3.40-3.30 (m, 2H), 1.95 (s, 3H), 1.74 (s,

3H), 1.60-1.45 (m, 2H), 1.24 (s, br, 21H), 0.88 (t, 3H, J=6.6Hz). ^{13}C NMR ($CDCl_3$): δ 170.53, 170.19, 138.17, 138.07, 137.98, 137.87, 130.81, 129.30, 128.58, 128.43, 128.36, 128.29, 128.09, 128.00, 127.95, 127.82, 127.70, 127.60, 113.54, 100.44, 99.91, 80.93, 78.46, 74.92, 74.78, 74.58, 74.29, 74.06, 73.50, 73.46, 71.77, 70.04, 69.39, 68.57, 55.30, 55.17, 51.15, 31.89, 29.66, 29.62, 29.54, 29.46, 29.32, 26.03, 23.50, 23.21, 22.65, 14.09. Fab MS: 1095 $(M+Na)^+$.

Dodecyl (2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-2-deoxy-β-D-glucopyranoside (TYC9)

To a solution of **TYC8** (0.85 g, 0.78 mmol) in 95% aqueous dichloromethane (15 mL) is added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.23 g, 1.01 mmol). The reaction mixture is stirred for 30 min. at room temperature. The reaction mixture is poured into a 10% solution of sodium bisulfite (30 mL) and dichloromethane (30 mL) is added. The organic layer is separated, washed with water (40 mL) and saturated brine (30 mL), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:DCM 5:5 to 8:2) to furnish **TYC9** (0.56 g, 74%) as a viscous liquid. TLC (EtOAc:DCM 7:3) Rf 0.48. ^1H NMR ($CDCl_3$): δ 7.35-7.20 (m, 20H), 7.20-7.10 (m, 2H), 5.83 (d, 1H, J=8.1Hz), 5.65 (d, 1H, J=8.4Hz), 4.80-4.40 (m, 13H), 4.00-3.40 (m, 17H), 1.96 (s, 3H), 1.75 (s, 3H), 1.60-1.50 (m, 2H), 1.24 (s, br, 22H), 0.88 (t, 3H, J=6.8Hz). ^{13}C NMR ($CDCl_3$): δ 170.35, 170.15, 138.61, 138.24, 137.68, 128.41, 128.40, 127.98, 127.86, 127.80, 127.67, 101.50, 100.36, 82.11, 81.83, 78.44, 74.84, 74.37, 74.02, 73.40, 71.96, 69.67, 68.84, 68.53, 56.90, 55.57, 31.89, 29.66, 29.62, 29.56, 29.42, 29.32, 25.94, 23.61, 23.29, 22.65, 14.09.

6 . 8 8 . Dodecyl (2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranoside (TYC10)

To a solution of TYC9 (0.39 g, 0.41 mmol) in THF-DMF (1:1 v/v, 16 mL) is added sodium hydride (39 mg, 1.63 mmol). The reaction mixture is stirred for 30 min. at room temperature. (S)-(-)-2-Bromopropionic acid (0.055 mL, 0.61 mmol) is added. The reaction mixture is stirred for 24 h at room temperature. The reaction mixture is poured into 2M hydrochloric acid (20 mL), and ethyl acetate (50 mL) is added. The organic layer is separated, washed with water (40 mL) and saturated brine (30 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (MeOH:DCM 1:9) to furnish TYC10 (0.26 g, 62%) as a viscous liquid. TLC (MeOH:DCM 1:9) Rf 0.36. ^1H NMR ($CDCl_3$, CD_3OD): δ 7.30-7.10 (m, 18H), 7.10-7.00 (m, 2H), 4.75-4.30 (m, 11H), 3.80-3.15 (m, 19H), 1.92 (s, 3H), 1.75 (s, 3H), 1.50-1.40 (m, 2H), 1.30-1.10 (m, 21H), 0.78 (t, 3H, J=6.8Hz). ^{13}C NMR ($CDCl_3$): δ 172.32, 171.56, 138.08, 137.62, 137.56, 128.30, 128.24, 128.20, 128.15, 128.10, 127.81, 127.76, 127.70, 127.58, 127.52, 127.48, 127.34, 101.71, 99.16, 81.61, 78.29, 77.86, 77.21, 75.40, 74.66, 74.42, 73.40, 73.11, 69.54, 69.24, 69.23, 55.62, 54.07, 31.71, 29.46, 29.30, 29.24, 29.14, 25.84, 25.69, 22.83, 22.55, 22.47, 18.81, 13.83. Fab MS: 1069 (M-H+Na+Na)⁺.

6 . 8 9 . Dodecyl (2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranoside (TYC11)

To a solution of TYC10 (0.26 g, 0.25 mmol) in ethanol (100 mL) is added 10% palladium on carbon (0.50 g). The reaction mixture is shaken at room temperature in a Parr hydrogenator for 24 h under a hydrogen atmosphere at 40 psig. The reaction mixture is filtered

through a membrane filter and concentrated. The crude product (0.15 g, 89%) is used in the next step without further purification. ^{1}H NMR (CD_3OD): δ 4.60-4.50 (m, 1H), 4.51 (d, 1H, J=8.4Hz), 4.34 (d, 1H, J=7.8Hz), 4.95-3.35 (m, 12H), 1.98 (s, 6H), 1.60-1.45 (m, 2H), 1.43 (d, 3H, J=6.6Hz), 1.28 (s, br, 20H), 0.89 (t, 3H, J=6.8Hz). ^{13}C NMR (CD_3OD): δ 173.92, 102.88, 101.64, 80.87, 78.31, 77.26, 76.01, 75.58, 72.65, 70.75, 63.23, 61.48, 57.65, 56.21, 33.03, 30.78, 30.72, 30.60, 30.50, 30.43, 27.73, 27.06, 26.98, 23.69, 23.06, 19.42, 14.44. Fab MS: 709 (M-H+Na+Na)$^+$.

6.9.0. Dodecyl (2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-acetyl-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranoside (TYC12)

To a solution of TYC11 (0.15 g, 0.23 mmol) in pyridine (10 mL) is added acetic anhydride (0.43 mL, 4.56 mmol). The reaction mixture is stirred for 2 h at room temperature. Ethyl acetate (100 mL) and 2M hydrochloric acid (100 mL) are added. The reaction mixture is stirred for 1 h at room temperature. The organic layer is separated, washed with water (50 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The crude product (0.16 g, 85%) is used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 5.15-5.05 (m, 2H), 4.70-3.90 (m, 9H, 3.90-3.20 (m, 8H), 2.10-1.90-(m, 18H), 1.60-1.50 (s, br, 2H), 1.40 (d, 3H, J=6.3Hz), 1.215 (s, br, 20H), 0.84 (6.6Hz). Fab MS: 832 (M-H+Na+Na)$^+$.

6.9.1. Methyl (3α,5β)-3-Methoxycholan-24-oate (TYC14)

To a soltuion of lithocholic acid (31.40 g, 83.5 mmol) in dimethylformamide (165 mL) is added sodium hydride (6.01 g, 0.25 mol). The reaction mixture is stirred for 30 min. at room temperature. Iodomethane

(15.6 mL, 0.25 mol) is added. The reaction mixture is stirred for 3 h at room temperature. The reaction mixture is poured into 2M hydrochloric acid (100 mL), and an ether-DCM solvent mixture (2:1 v/v, 500 mL) is added. The organic layer is separated, washed with saturated brine (200 mL) and saturated aqueous potassium carbonate solution (200 mL), then dried (Na_2SO_4) and concentrated. The crude product (Qy) is used in the next step without further purification. ^1H NMR ($CDCl_3$): δ 3.66 (2, 3H), 3.35 (s, 3H), 3.20-3.10 (m, 1H), 2.40-2.15 (m, 2H), 2.00-1.50 (m, 12H), 1.45-0.95 (m, 18H), 0.91 (s, 3H), 0.90 (d, 3H, J=6Hz), 0.63 (s, 3H).

6.92. (3α,5β)-3-Methoxycholan-24-ol (TYC15)

To a cooled (0 °C) solution of TYC14 (37.43 g, 92.6 mmol) in THF-ether solvent mixture (2:1 v/v, 450 mL) is added lithium aluminium hydride (7.04 g, 0.185 mol). The reaction mixture is stirred for 2 h at 0 °C. The reaction mixture is quenched by dropwise addition of 1M sodium hydroxide solution. The reaction mixture is poured into 2M hydrochloric acid (200 mL), and diethyl ether (300 mL) is added. The organic layer is separated, washed with water (200 mL) and saturated brine (200 mL), then dried (Na_2SO_4) and concentrated. A solvent mixture of EtOAc-hexane (3:7 v/v, 400 mL) is added to the residue. The resulting white precipitate is filtered off. The filtrate is concentrated. The residue is crystallized from methanol-water to furnish TYC15 as a white solid. The crude product (17.26 g, 55%) is used in the next step without further purification. TLC (EtOAc-Hexane 1:1) Rf 0.63. ^1H NMR ($CDCl_3$): δ 3.60 (t, 2H, J=6.2Hz), 3.34 (s, 3H), 3.20-3.10 (m, 1H), 2.00-1.50 (m, 10H), 1.50-0.95 (m, 21H), 0.91 (s, 3H), 0.91 (d, 3H, J=6.6Hz), 0.63 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 80.41, 63.59, 56.46, 56.13, 55.23, 42.68, 42.03, 40.32, 40.17, 35.83,

35.59, 35.29, 34.87, 32.74, 31.79, 29.42, 28.30, 27.31, 26.76, 26.39, 24.21, 23.41, 20.79, 18.61, 12.02.

**6 9 3
(3α,5β)-24-(6-O-Benzyl-2-deoxy-3-O-p-methoxybenzyl-2-N-phthalimido-β-D-glucopyranosyloxy)-3-methoxycholane (TYC16)**

A solution of **TYC15** (7.09 g, 18.8 mmol), **TYC3** (13.17 g, 18.8 mmol) and 2,6-di-tert-butyl-4-methylpyridine (3.86 g, 18.8 mmol) in EtOAc-hexane solvent mixture (1:1 v/v, 190 mL) is added dropwise into a cooling bath (-40 °C) followed quickly by the addition of trifluoromethanesulfonic anhydride (3.74 mL, 31.0 mmol). The reaction mixture is stirred for 30 min. at -40 °C. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (100 mL). The organic layer is separated, and the aqueous layer is extracted with ethyl acetate (100 mL). The combined organic layers is washed with water (200 mL) and saturated brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue is extracted with a sovent mixture of EtOAC-hexane (3:7 v/v, 200 mL). The filtrate is concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7 to 5:5) to furnish **TYC16** (2.54 g, 15%) as a viscous liquid. TLC (EtOAc-Hexane 1:1) Rf 0.66. ^1H NMR ($CDCl_3$): δ 7.90-7.60 (m, 6H), 7.40-7.25 (m, 6H), 6.96 (d, 2H, J=8.7Hz), 6.43 (d, 2H, J=8.7Hz), 5.10 (d, 1H, J=8.4Hz), 4.70-4.50 (m, 4H), 4.45 (d, 1H, J=12.0Hz), 4.25-4.05 (m, 3H), 3.85-3.70 (m, 5H), 3.70-3.50 (m, 2H), 3.60 (s, 3H), 3.34 (s, 3H), 3.30-3.20 (m, 1H), 3.20-3.10 (m, 1H), 3.04 (d, 1H, 2.4Hz), 1.90-1.50 (m, 7H), 1.50-0.80 (m), 0.87 (s, 3H), 0.63 (d, 3H, J=6.3Hz), 0.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.74, 137.62, 133.61, 130.34, 129.46, 128.41, 127.78, 127.71, 113.37, 98.51, 80.35, 78.34, 74.46, 76.85, 73.62, 73.52, 70.72, 70.33, 56.26, 55.94, 55.50, 55.40, 54.81, 42.44, 41.94, 40.23, 39.99, 35.70, 35.35, 34.79, 32.71,

32.01, 27.89, 27.25, 26.69, 26.35, 26.05, 24.08, 23.33, 20.65, 18.16, 11.82. Fab MS: 900 $(M+Na)^+$.

**6 9 4
(3α,5β)-24-[(2-Deoxy-2-N-phthalimido-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-deoxy-6-O-benzyl-3-O-p-methoxybenzyl-2-N-phthalimido-β-D-glucopyranosyloxy]-3-methoxycholane (TYC17)**

To a cooled (-40 °C) solution of **TYC16** (2.15 g, 2.45 mmol), **TYC6** (4.66 g, 6.78 mmol) and 2,6-di-tert-butyl-4-methylpyridine (1.76 g, 8.59 mmol) in EtOAc-hexane (1:1 v/v, 50 mL) is added trifluoromethanesulfonic anhydride (0.82 mL, 6.81 mmol). The reaction mixture is stirred for 30 min. at -40 °C. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (50 mL). The organic layer is separated, and the aqueous layer is extracted with ethyl acetate (30 mL). The combined organic layers is washed with water (60 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (EtOAc:Hexane 3:7 to 5:5). The resulting product (3.26 g) is used in the next step without further purification. TLC (EtOAc:Hexane 3:7) Rf 0.25. TLC (EtOAc:Hexane 1:1) Rf 0.60. Fab MS: 1462 $(M+H+Na)^+$.

**6 9 5
(3α,5β)-24-[(2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-2-deoxy-3-O-p-methoxybenzyl-β-D-glucopyranosyloxy]-3-methoxycholane (TYC18)**

A solution of **TYC17** (crude, 3.26 g) and hydrazine hydrate (4.39 mL, 90.6 mmol) in a solvent mixture of 95% EtOH-THF (1:1 v/v, 40 mL) is heated under reflux for 24 h. White precipitate is filtered off and the filtrate is concentrated. The residue is dissolved in pyridine (20 mL) and acetic anhydride (4.27 mL, 45.3 mmol) is added. The reaction mixture is stirred for 2 h at room temperature. Methanol (3.67 mL, 90.7 mmol) is added.

The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (50 mL), and ethyl acetate (100 mL) is added. The organic layer is separated, washed with water (50 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue is washed with EtOAc-hexane mixed solvent (6:4 v/v) to furnish **TYC18** as a white solid. The crude product (1.92 g) is used in the next step without further purification. Fab MS: 1286 $(M+H+Na)^+$.

6 . 9 6 . (3α,5β)-24-[(2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-2-deoxy-β-D-glucopyranosyloxy]-3-methoxycholane (TYC19)

To a solution of **TYC18** (crude, 1.92 g) in 95% aqueous dichloromethane (30 mL) is added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.45 g, 1.98 mmol). The reaction mixture is stirred for 30 min. at room temperature. The reaction mixture is poured into a 10% solution of sodium bisulfite (30 mL), and dichloromethane (30 mL) is added. The organic layer is separated, washed with water (40 mL) and saturated brine (30 mL), then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (MeOH:DCM 5:95) to furnish **TYC9** (0.62 g, 19% from **TYC16**) as a viscous liquid. TLC (MeOH-DCM 1:9) Rf 0.50. ^1H NMR ($CDCl_3$): δ 7.35-7.20 (m, 18H), 7.20-7.10 (m, 2H), 5.56 (d, 1H, J=7.5Hz), 4.91 (d, 1H, J=8.7Hz), 4.80-4.65 (m, 4H), 4.60-4.40 (m, 7H), 4.05-3.95 (m, 1H), 3.85-3.75 (m, 1H), 3.75-3.40 (m, 8H), 3.34 (s, 3H), 3.20-3.10 (m, 1H), 1.97 (s, 3H), 1.90-1.60 (m, 5H), 1.68 (s, 3H), 1.45-1.25 (m, 7H), 1.15-0.95 (m, 6H), 0.90 (s, 3H), 0.87 (d, 3H, J=6.6Hz), 0.61 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.49, 170.35, 138.79, 138.46, 138.37, 137.76, 137.69, 128.50, 128.25, 128.17, 127.82, 127.77, 127.74, 127.68, 127.61, 127.52, 127.46, 127.31, 126.59,

101.98, 100.73, 83.03, 82.36, 80.30, 78.51, 75.04, 74.71, 74.10, 73.23, 72.81, 70.04, 68.98, 56.32, 56.10, 55.40, 42.54, 41.93, 40.21, 40.05, 35.71, 35.19, 34.77, 32.65, 31.93, 28.22, 27.23, 26.68, 26.30, 24.12, 23.51, 23.33, 23.20, 20.69, 18.47, 11.93. Fab MS: 1166 (M+H+Na)$^+$.

(3α,5β)-24-[(2-Acetamido-2-deoxy-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-benzyl-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranosyloxy]-3-methoxycholane (TYC20)

To a solution of **TYC19** (0.54 g, 0.47 mmol) in THF-DMF (2:1 v/v, 9 mL) is added sodium hydride (68 mg, 2.83 mmol). The reaction mixture is stirred for 30 min. at room temperature. (S)-(-)-2-Bromopropionic acid (0.064 mL, 0.71 mmol) is added. The reaction mixture is stirred for 24 h at room temperature. The reaction mixture is poured into 2M hydrochloric acid (20 mL), and ethyl acetate (50 mL) is added. The organic layer is separated, washed with water (40 mL) and saturated brine (30 mL), then dried (Na_2SO_4) and concentrated. The crude product (0.57 g) is used in the next step without further purification. TLC (MeOH:DCM 1:9) Rf 0.25. Fab MS: 1260 (M+Na+Na)$^+$.

(3α,5β)-24-[(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranosyloxy]-3-methoxycholane (TYC21)

To a solution of **TYC20** (crude, 0.57 g) in ethanol (100 mL) is added 10% palladium on carbon (0.57 g). The reaction mixture is shaken at room temperature in a Parr hydrogenator for 24 h under a hydrogen atmosphere at 40 psig. The reaction mixture is filtered through a membrane filter and concentrated. The crude product (0.39 g, 96% from **TYC19**) is used in the next step without

further purification. ^{1}H NMR (CD_3OD): δ 4.41 (d, 1H, J=8.1Hz), 4.28 (d, 1H, J=8.1Hz), 3.80-3.30 (m, 12H), 3.12 (s, 3H), 3.20-2.90 (m, 6H), 2.01 (s, 3H), 1.91 (s, 3H), 1.85-1.30 (m, 10H), 1.23 (d, 3H, J=6.9Hz), 1.30-1.10 (m, 9H), 1.10-0.80 (m, 10H), 0.74 (s, 3H), 0.72 (d, 3H, J=6.9Hz), 0.47 (s, 3H). ^{13}C NMR (CD_3OD): δ 176.90, 101.79, 101.08, 81.90, 80.68, 78.42, 77.16, 76.77, 76.25, 75.29, 72.58, 71.89, 71.22, 66.81, 63.07, 58.41, 58.29, 57.85, 57.51, 55.83, 43.81, 43.32, 41.83, 41.48, 37.15, 36.72, 36.24, 35.89, 33.84, 33.24, 29.36, 28.34, 27.78, 37.60, 25.24, 23.94, 21.91, 19.15, 18.35, 15.44, 12.54. Fab MS: 899 (M-H+Na+Na)$^+$.

(3α,5β)-24-[(2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-6-O-acetyl-3-O-(1-carboxy)ethyl-2-deoxy-β-D-glucopyranosyloxy]-3-methoxycholane (TYC2)

To a solution of TYC21 (crude, 0.39 g) in pyridine (10 mL) is added acetic anhydride (0.86 mL, 9.12 mmol). The reaction mixture is stirred for 2 h at room temperature. Ethyl acetate (100 mL) and 2M hydrochloric acid (100 mL) are added. The reaction mixture is stirred for 1 h at room temperature. The organic layer is separated, washed with water (50 mL) and saturated brine (50 mL), then dried (Na_2SO_4) and concentrated. The crude product (0.41 g, 87%) is used in the next step without further purification. TLC (MeOH:DCM 1:9) Rf 0.47. ^{1}H NMR ($CDCl_3$): δ 7.08 (d, 1H, J=7.2Hz), 6.50 (d, 1H, J=9.6Hz), 5.10-4.95 (m, 2H), 4.61 (d, 1H, J=6.9Hz), 4.41 (d, 1H, J=8.4Hz), 4.40-3.90 (m, 5H), 3.75-3.35 (m, 5H), 3.28 (s, 3H), 3.15-3.05 (m, 1H), 2.05-1.85 (m, 18H), 1.80-1.40 (m, 7H), 1.40-0.90 (m, 11H), 1.30 (d, 3H, J=6.6Hz), 0.84 (s, 3H), 0.81 (d, 3H, J=6.3Hz), 0.55 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.75, 171.24, 170.96, 170.84, 170.51, 169.28, 102.00, 100.93, 80.38, 77.66, 76.85, 74.60, 73.00, 72.75, 71.74, 70.24, 68.07, 62.73, 61.60,

56.54, 56.04, 55.32, 54.12, 42.56, 41.92, 40.22, 40.05, 35.72, 35.43, 35.17, 34.76, 32.58, 31.77, 28.19, 27.21, 26.61, 26.28, 25.97, 24.10, 23.30, 23.22, 22.93, 20.89, 20.68, 20.51, 18.45, 28.29, 11.92. Fab MS: 1073 (M+5H+Na+Na)'.

7. General Procedure For Coupling To Support-Bound Peptide, Deprotection Of Sugar And Cleavage From The Resin

An Fmoc-protected resin-bound peptide building block, R-P, is first swollen in DMF (2 mL, 380 rpm, 0.5 h). The Fmoc group is cleaved off (2 mL of 20% piperidine in DMF, 380 rpm, 0.5 h). Subsequently, the deprotected R-P is washed with fresh DMF four times (2 mL, 380 rpm, 5 min/wash). The R-P (1.0 equiv) is then treated with the free acid of an S-L building block (1.0-3.0 equiv) in the presence of an activating or coupling agent with agitation for about 4 h. Any of four different coupling agent-solvent combinations ("coupling cocktails") are used: EEDQ-DCM, HATU-DIPEA/DMF, HBTU-DIPEA/DMF, or PyBOP-DIPEA/DMF. (See, Fig. 3 for the structures of the activating agents.)

After the coupling reaction is complete, the coupling cocktail is filtered off and the resin is washed four times with fresh 2 mL portions of DMF (380 rpm, 5 min/wash). The sugar protecting groups (e.g., acetyl groups, pivaloyl groups) are removed by treating the resin with a solution of sodium methoxide in a solvent mixture of methanol-DMF (1:1, v/v) with agitation (380 rpm) for ca. 15-24 h. After filtration, the resin is washed four times with fresh 2 mL portions of the methanol-DMF solvent mixture (380 rpm, 5 min/wash), followed by four 2 mL portions of DCM (380 rpm, 5 min/wash).

The dichloromethane is removed, and the sugar-deprotected resin is next treated with a 90% solution of TFA in water (2 mL, 380 rpm, ca. 2 h). The desired

product is obtained from the product solution. Residual resin may be treated a second time with 90% TFA-H_2O (1 mL, 380 rpm, 15 min). A second product solution may hence be obtained, which is combined with the first product solution. The trifluoroacetic acid-water solvent is removed by evaporation in a block heater at 40 °C using an air stream.

The addition of diethyl ether (4 mL) precipitates the product lipoglycopeptide. The resulting mixture is centrifuged at 4 °C (4000 rpm, 10 min). The solvent is then removed by suction using a pipette, and the product is subsequently washed with an additional 2 mL of diethyl ether. The centrifuging and pipetting steps are repeated once or twice more. Finally, the desired product is isolated and dried in a vacuum dessicator.

These general steps are illustrated in Fig. 2 and more specifically in Fig. 6 or Fig. 8.

The solid support-bound peptides are prepared using known methods using, for example, a Merrifield resin (polystyrene/1% divinylbenzene copolymer) and an acid labile chlorotrityl linker group. Alternatively, the building blocks may be obtained from commercial sources, such as Advanced ChemTech (Kentucky, U.S.A.).

The following illustrates a specific example of coupling a support-bearing peptide to a lipid-bearing sugar, deprotection and cleavage.

7.1 Solid phase synthesis of peptidoglycan monomers 52 and 53

The solid phase synthesis of peptidoglycan monomer analogous **52** and **53** is illustrated in Fig. 8. The lipid-bearing disaccharide sugar **8** is coupled to a tripeptide bound to polystyrene resin via a chlorotrityl linker, AKA-(Clt)-(PS). The lipid-bearing monosaccharide sugar **51** is coupled to AKA-(Clt)-(PS) as well as to a tripeptide bound to polyethylene glycol grafted

polystyrene resin, AKA-(PEG)-(PS). Solid phase coupling reactions are carried out with two equivalents of the glycocarboxylic acid, 8 or 51, and two equivalents of the coupling reagent. The reaction mixtures are then shaken for four hours at room temperature.

The resin-bound monosaccharide coupled products, 51-AKA-(Clt)-(PS) and 51-AKA-(PEG)-(PS), are treated with 90% aqueous trifluoracetic acid to complete the cleavage and global deprotection process. The monosaccharide peptidoglycan monomer 52 is obtained by precipitation with diethyl ether [Fab MS: 819 (M-H + 2Na)$^+$].

The disaccharide coupled product, 8-AKA-(Clt)-(PS), is first treated with sodium methoxide to remove the acetate protecting groups. It is followed by the 90% TFA cleavage and peptide deprotection step. The disaccharide peptidoglycan monomer 53 is finally precipitated with diethyl ether [Fab MS: 991 (M-H + 2Na)$^+$]. The coupling yield of each combination of solid support and coupling reagent is determined by RP-HPLC analysis of the isolated products. RP-HPLC analysis is performed on a C18 column (5 micron, 4.6x250mm) with gradient elution (10% to 50% acetonitrile, water/0.1% TFA) and monitored by UV (205 nm) and ELSD (evaporative light scattering detector). The results (percent yields) are summarized in Table 1.

Table 1

	51 + AKA-(Clt)-(PS)	51 + AKA-(PEG)-(PS)	8 + AKA-(Clt)-(PS)
EEDQ/DCM	74%	80%	67%
HATU/DIPEA/DMF	84%	85%	89%
HBTU/DIPEA/DMF	79%	77%	89%
PyBOP/DIPEA/DMA	75%	76%	82%

7.2Solid phase synthesis of peptidoglycan monomer 54

Another method for the synthesis of peptidogylcan monomers is seen in Fig. 6. An Fmoc-protected peptide building block, Fmoc-[L-Ala]-[L-Lys]-[D-Ala]-(R), is deprotected in the manner described in the general procedures. The deprotectd peptide is coupled to the pentafluorophenyl (Pfp) ester of the lipid-sugar by Dhbt-OH. The deprotection and cleavage steps are as described in the general procedure to yield 54.

8. Lipoglycopeptide Synthesis Assay

A peptidoglycan polymerization assay is adapted from one described by Mirelman et al., in *Biochemistry* (1976) 15:1781-1790 and modified by Allen et al., in *FEMS Microbiol. Lett.* (1992) 98:109-116. Briefly, *E. coli* (ATCC Cat. No. 23226) are permeabilized with ether to permit exogenously added radiolabeled and non-radiolabeled cell wall precursors to penetrate the bacterial cell wall. Screening quantities of UDP muramyl-pentapeptide (UDP-N-acetylmuramyl-L-Ala-D-Glu-*meso*-diaminopimelyl-D-Ala-D-Ala) are isolated from an aqueous extract of *B. cereus* (ATCC Cat. No. 11778) according to a published method. See, Kohlrausch and Holtje, *FEMS Microbiol. Lett.* (1991) 78:253-258; Kohlrausch et al., in *J. Gen. Microbiol.* (1989) 153:1499-1506. Bacterial protein is determined by the method of Bradford, in *Anal. Biochem.* (1976) 72:248.

Polymerization assays are conducted in 96-well filter-bottom plates (Millipore GF/C - Cat. No. MAFC NOB 10). In a final assay volume of 100 μL, each well contains: 50 mM Tris - HCl (pH 8.3); 50 mM NH_4Cl; 20 mM $MgSO_4$* 7 H_2O; 10 mM ATP (disodium salt); 0.5 mM β-mercaptoethanol; 0.15 mM D-aspartic acid; 0.001 mM UDP-N-acetyl [^{14}C-]-D-glucosamine (DuPont/N.E.N. - 307 mCi/mmol); 0.01 mM UDP-MurNAc-pentapeptide, 100 μg/mL

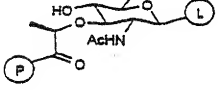
tetracycline and 10 μg/well ether-treated bacterial protein.

Novel test compounds are solubilized in distilled water and screened at a final assay concentration of 100 μg/mL. With the exception of radiolabel and isolated native pentapeptide, all remaining biochemicals are available from Sigma.

Reactions are begun by adding 10 μL aliquots of bacterial protein in assay buffer into wells containing all remaining reagents. Plates are covered, mixed for 30 seconds, then incubated at 37 °C for 2 hr. Ice cold 20% TCA (100 μL) is added to each well. Plates are gently mixed (60 sec), then refrigerated (4 °C) for 30 min to assure precipitation of all peptidoglycan.

Plates are placed under vacuum filtration on a Millipore manifold, flitered and washed 4-5 times with 200 μL/well of 10% TCA. Filters are punched into scintillation vials, filled with Cytoscint (ICN), capped, shaken and counted using a Beckman LS6000 spectrometer. Percent inhibition of incorporation of ^{14}C-label into peptidoglycan is computed from control (total incorporation) and background (blank) wells containing 300 μg/mL of vancomycin, which completely inhibited incorporation of radiolabel. All wells are arrayed in duplicates, which usually varied by <20%. Concentration-response curves for vancomycin are arrayed on each plate as positive controls (IC_{50} for inhibition of incorporation = 2.4 ± 0.2 μg/mL; n = 7).

The results of the assay indicated that at least three members of the library exhibited inhibitory activity. Decoding of the library reveals that all three compounds bear the same S-L building block, shown below.

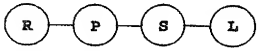


The peptide portion of the three compounds exhibiting inhibitory activity are: L-S-(L-Ala-D-iso-Gln-L-Lys-D-Ala-OH), L-S-(L-Lys-D-Ala-D-Ala-OH) and L-S-(Gly-D-iso-Gln-L-Lys-D-Ala-D-Ala-OH).

Doubtless, other embodiments of the present invention will be apparent to those of ordinary skill in the art. Such embodiments, while not specifically described herein, nevertheless fall within the scope and spirit of the invention, which is not limited by the specific embodiments described but only by the following claims.

WHAT IS CLAIMED IS:

1. A solid phase lipoglycopeptide library comprising a plurality of distinct substances of the formula



in which the group R comprises a solid support, the group P comprises one or more amino acids, peptides, or polypeptides, the group S comprises one or more sugars and the group L comprises one or more lipids.

2. The library of claim 1 in which more than one copy of each distinct substance is present.

3. The library of claim 1 in which at least one member of each group of the formula is covalently attached to at least one member of an adjacent group.

4. The library of claim 3 in which the same sugar of the group S is covalently attached to at least one member of the group P and to at least one member of the group L.

5. The library of claim 3 in which at least one sugar of the group S is covalently attached to a lipid of the group L through a covalent bond comprising a glycosidic bond.

6. The library of claim 3 in which at least one sugar of the group S is covalently attached to a lipid of the group L through an anomeric alpha-hydroxy acetamide bond.

7.The library of claim 4 in which at least one sugar of the group S is covalently attached to a member of the group P through a C-3 hydroxy alpha-acetamido or alpha-propionamido moiety.

8.The library of claim 3 in which the covalent attachment is made through a linker.

9.The library of claim 4 in which the linker is labile.

10.The library of claim 4 in which the linker is acid labile or photolabile.

11.The library of claim 4 in which at least one member of the group P is bound to the resin by a halotrityl moiety.

12.The library of claim 11 in which the halotrityl moiety is a chlorotrityl moiety.

13.The library of claim 4 in which at least one member of the group P is bound to the resin by an alpha-bromo-alpha-methylphenacyl moiety.

14.The library of claim 3 in which the covalent attachment comprises one or more amine, ether, thioether, ester, thioester, amide, acetamide, phosphate, phosphonate, phosphinate, or sulfate bonds.

15.The library of claim 14 in which the covalent attachment comprises one or more glycosidic bonds.

16.The library of claim 1 in which the solid support is comprised of an insoluble polymer, metal, or glass surface.

17.The library of claim 1 in which the amino acid, peptide, or polypeptide is comprised exclusively or predominantly of hydrophilic amino acid residues.

18.The library of claim 1 in which the amino acid, peptide, or polypeptide is comprised exclusively or predominantly of hydrophobic amino acid residues.

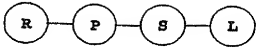
19.The library of claim 1 in which the sugar may be a monosaccharide, disaccharide, or polysaccharide.

20.The library of claim 19 in which the monosaccharide is comprised of a hexose, pentose, deoxy analog thereof, dideoxy analog thereof, azido-substituted analog thereof, or amino-substituted analog thereof.

21.The library of claim 19 in which the disaccharide or polysaccharide is comprised of hexoses, pentoses, deoxy analogs thereof, dideoxy analogs thereof, azido-substituted analogs thereof, amino-substituted analogs thereof, or combinations thereof.

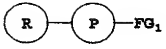
22.The library of claim 1 in which the lipid is comprised of a saturated, unsaturated, or polyunsaturated linear, branched or cyclic aliphatic group comprising 2-60 carbon atoms.

23.A method of preparing a solid phase lipoglycopeptide library having a plurality of distinct substances of the formula



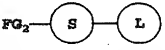
comprising:

(a) providing one or more groups R, P and FG_1 of the formula



in which R comprises a solid support to which is bound the group P comprising one or more amino acids, peptides, or polypeptides, at least one member of the group P bearing the first functional group FG_1 capable of participating in a bond-forming reaction;

(b) providing one or more groups S, L and FG_2 of the formula



in which S comprises one or more sugars to at least one of which is bound a group L comprising one or more lipids, at least one sugar of the group S bearing the second functional group FG_2 capable of participating in the bond-forming reaction;

(c) combining the one or more groups R, P and FG_1 and the one or more groups S, L and FG_2 such that the bond-forming reaction takes place to form a bond between that member of the group P, which bore the first functional group FG_1, to that sugar of the group S, which bore the second functional group FG_2.

24. The method of claim 23 which further comprises soaking the solid support in an organic solvent prior to the combination step.

25. The method of claim 23 which further comprises removing any protecting group present on the first functional group FG_1 prior to the combination step.

26. The method of claim 23 in which the combination step includes providing an activating agent to facilitate the bond-forming reaction.

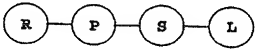
27. The method of claim 23 removing any protecting groups present on groups P, S, or L.

28. The method of claim 23 which further comprises screening the resulting lipoglycopeptide library for one or more active substances.

29. The method of claim 23 which further comprises cleaving the group P from the group R.

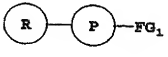
30. The method of claim 29 which further comprises recovering one or more substances released from the group R.

31. A method of preparing a solid phase lipoglycopeptide library having a plurality of distinct substances of the formula



comprising:

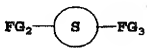
(a) providing one or more groups R, P and FG_1 of the formula



in which R comprises a solid support to which is bound the group P comprising one or more amino acids, peptides, or polypeptides, at least one member of the

group P bearing the first functional group FG_1 capable of participating in an initial bond-forming reaction;

(b) providing one or more groups S, FG_2, and FG_3 of the formula



in which S comprises one or more sugars, at least one sugar of the group S bearing the second functional group FG_2 capable of participating in the initial bond-forming reaction and the same or another sugar of the group S bearing the third functional group FG_3 capable of participating in a subsequent bond-forming reaction;

(c) combining the one or more groups R, P and FG_1 and the one or more groups S, FG_2, and FG_3 such that the initial bond-forming reaction takes place to form a bond between that member of the group P, which bore the first functional group FG_1, to that sugar of the group S, which bore the second functional group FG_2 to provide one or more initial bond-forming reaction products;

(c) providing one or more groups L and FG_4 of the formula

in which the group L comprises one or more lipids, at least one lipid of the group L bearing the fourth functional group FG_4 capable of participating in the subsequent bond-forming reaction;

(d) combining the one or more initial bond-forming reaction products and the one or more groups L and FG_4 such that the subsequent bond-forming reaction takes

place to form a bond between that member of the group S, which bore the third functional group FG_3, to that lipid of the group L, which bore the fourth functional group FG_4.

32. The method of claim 31 in which the one or more groups S, L and FG_2 are combined with the one or more groups R, P and FG_1 at room temperature in a solvent in the presence of an activating agent.

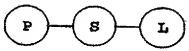
33. The method of claim 31 in which FG_2 comprises a pentafluorophenyl ester.

34. The method of claim 31 in which the activating agent comprises EEDQ, HATU, HBTU, or PyBOP.

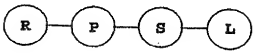
35. The method of claim 31 in which FG_2 comprises a carboxylic acid and FG_1 comprises an amine.

36. The method of claim 31 in which FG_1 is located on the side chain of a member of the group P.

37. A composition of the formula



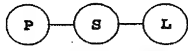
which is obtained from a substance of the formula



by cleaving the group P from the group R, in which the group R comprises a solid support, the group P comprises one or more amino acids, peptides, or

polypeptides, the group S comprises one or more sugars and the group L comprises one or more lipids.

38.A synthetic composition of the formula



in which the group P comprises one or more amino acids, peptides, or polypeptides, the group S comprises one or more sugars and the group L comprises one or more lipids.

39.The composition of claim 38 in which P comprises two or more amino acids in sequence.

40.The composition of claim 39 in which P comprises one or more peptides or polypeptides.

41.The composition of claim 40 in which each peptide or polypeptide comprises three or more amino acids in sequence.

42.The composition of claim 38 in which the lipid is comprised of a saturated, unsaturated, or polyunsaturated linear, branched or cyclic aliphatic group comprising 2-60 carbon atoms.

43.The composition of claim 38 in which the lipid is comprised of a saturated, unsaturated, or polyunsaturated linear, branched or cyclic aliphatic group comprising 4-50 carbon atoms.

44.The composition of claim 38 in which the lipid is comprised of a saturated, unsaturated, or

polyunsaturated linear, branched or cyclic aliphatic group comprising 10-30 carbon atoms.

45.The composition of claim 38 in which the lipid is comprised of substituted or unsubstituted aromatic or heteroaromatic groups.

46.The composition of claim 38 which is synthesized by a combinatorial approach.

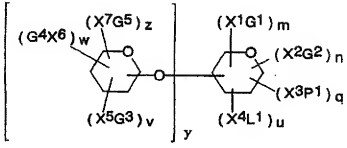
47.The composition of claim 38 which does not correspond with the structure of a naturally occurring lipid linked glycopeptide intermediate.

48.The composition of claim 38 in which the group L, if comprising a single lipid, does not include an undecaprenyl group.

49.The composition of claim 38 in which at least one sugar of the group S is covalently attached to at least one lipid of the group L.

50.The composition of claim 48 in which the covalent attachment comprises a glycosidic ether bond, phosphate, pyrophosphate, phosphinyl, phosphanyl, phosphonate, phosphonyl, phosphono, phosphino, phosphanoacetate, phosphonyl formate, phosphoramidyl phosphorothioate, phosphonylsulfonate, or phonphonylsulfonate bond.

51.A compound of the formula:



in which

L^1 comprises a lipid group;

P^1 comprises one or more amino acids, peptides or polypeptides;

G^1, G^2, G^3, G^4, or G^5 can each independently be a substituted or unsubstituted, branched or unbranched alkyl, alkoxy, alkenyl, C1-C8 acyl, acetyl, alkoxycarbonyl, hydroxyalkyl, carboxyalkyl group or a substituted or unsubstituted aromatic or heteroaromatic group, or hydrogen;

X^1, X^2, X^5, X^6 or X^7 can each independently be a functional group comprising an oxyalkyl, amine, ether, thioether, ester, thioester, amide, acyl, acetamido, phosphate, phosphinate, pyrophosphate, sulfate, azido, hydroxy group or hydrogen, provided that if the functional group is azido, hydroxy, or hydrogen the attached G group is not present;

X^3 or X^4 can each independently be a functional group comprising an amine, ether, thioether, ester, thioester, amide, acetamide, acyl, phosphate, phosphinate, pyrophosphate, sulfate group;

y is 0, 1, 2, or 3;

m, n, v, w, or z can independently be 0, 1, 2, or 3 provided that the sum of m and n is not greater than 3 or the sum of v , w and z is not greater than 5;

q or u can independently be 1, 2, or 3 provided that the sum of q and u is not greater than 5;

provided that the compound is not 2-N-Acetyl-1-α-O-allyl-4,6-O-isopropylidenemuramyl-L-alanyl-D-glutamine benzylester; (2R)-Benzyl 2-[N-(2'-N-Acetyl-1'-α-O-allyl-4',6'-O-acetylmuramyl-L-alanyl)amino]-4-cyanobutanoate; (2R) Benzyl 2-N-Acetyl-1'-α-O-allyl-4,6-O-isopropylidenemuramyl-L-alanyl)amino]-4-cyanobutanoate; (2R,2''R)-Benzyl 2-[N-[2'-N-Acetyl-1'-α-O-[(N,N-diisopropylamino)(butoxy)phosphinyl]-4',6'-di-O-acetylmuramyl-L-alanyl]amino]-4-cyanobutanoate; (2R,2''R)-Benzyl 2-[N-[2'-N-Acetyl-1'-α-O-[[2''-carbobenzoxy-2''-(pentyloxy)ethoxy](benzyloxy)phosphoryl]-4',6'-di-O-acetylmuramyl-L-alanyl]amino]-4-cyanobutanoate; (2R,2''R)-2-[N-[2'-N-Acetyl-1'-α-O-[[2''-carboxy-2''-(pentyloxy)ethoxy]hydroxyphosphoryl]muramyl-L-alanyl]-amino]-4-cyanobutanoate; or the natural substrate for either the transglycosylase activity of penicillin binding proteins or the N-acetylglucosaminyl transferase activity of the murG gene product.

52. The compound of claim 51 in which X^1G^1 or X^2G^2 can be located on position 2 or 5, X^3P^1 is located on position 3, and X^4L^1 is located on position 1 of the ring.

53. The compound of claim 51 in which X^1G^1, X^5G^3, X^6G^5, or X^7G^4 can be a hydroxyl, $HOCH_2CH_2$-, acetamide, phthalimido, benzoyl, alkoxybenzoyl, alkoxycarbonylalkyl, carboxyalkyl, or pivaloyl group.

54. The composition of claim 51 in which P^1 comprises one or more peptides or polypeptides.

55. The composition of claim 54 in which each peptide or polypeptide comprises three or more amino acids in sequence.

56. The composition of claim 51 in which L^1 is comprised of a saturated, unsaturated, or polyunsaturated linear, branched or cyclic aliphatic group comprising 4-30 carbon atoms.

57. The composition of claim 51 in which L^1 is comprised of substituted or unsubstituted aromatic or heteroaromatic groups.

58. The composition of claim 51 in which the covalent attachment of X^4 comprises a glycosidic ether bond, phosphate, pyrophosphate, phosphinyl, phosphanyl, phosphonate, phosphonyl, phosphono, phosphino, phosphanoacetate, phosphonyl formate, phosphoramidyl phosphorothioate, phosphonylsulfonate, or phonphonylsulfonate bond.

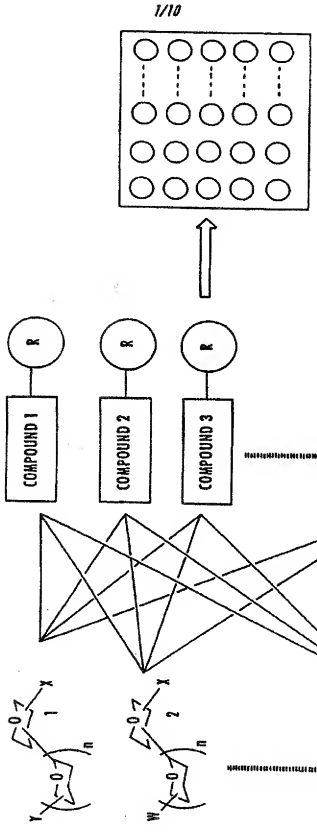

GLYCOCONJUGATE LIBRARY
COMPOUND 1
COMPOUND 2
COMPOUND 3
COMPOUND N
R
R
R
R
X
O
1
n
Y
O
X
O
2
n
W
O
X
O
N
n
Z
O

Figure 1

SOLID-PHASE CHEMISTRY

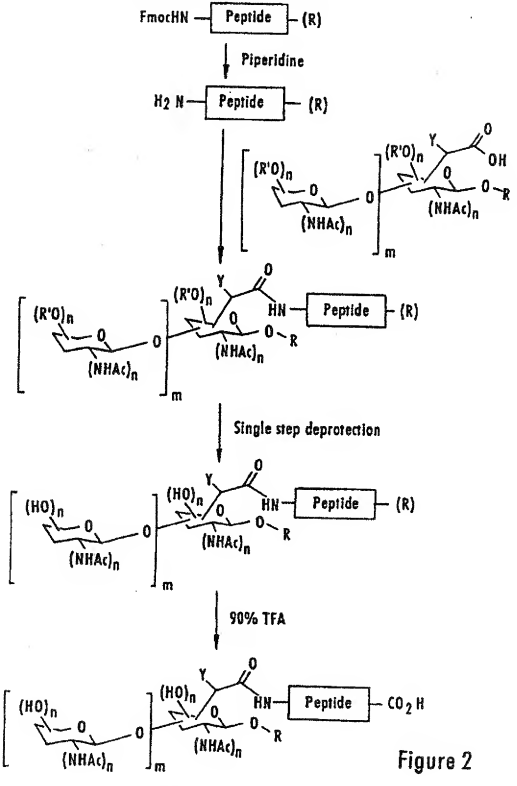


Figure 2

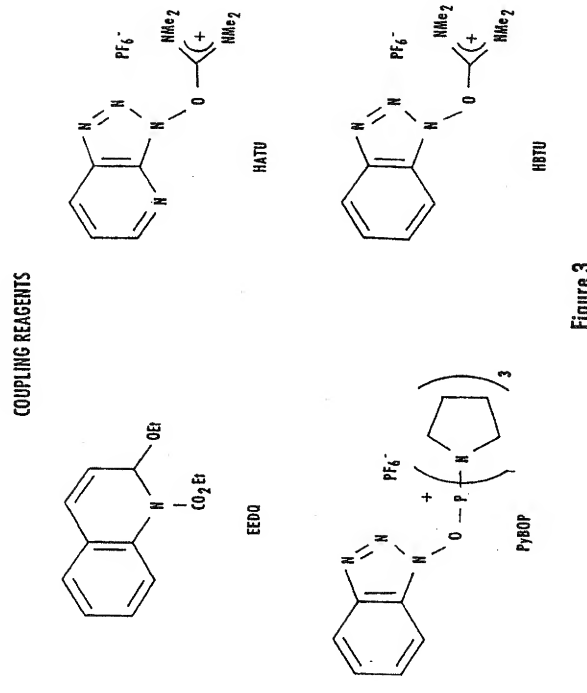


Figure 3

Figure 4

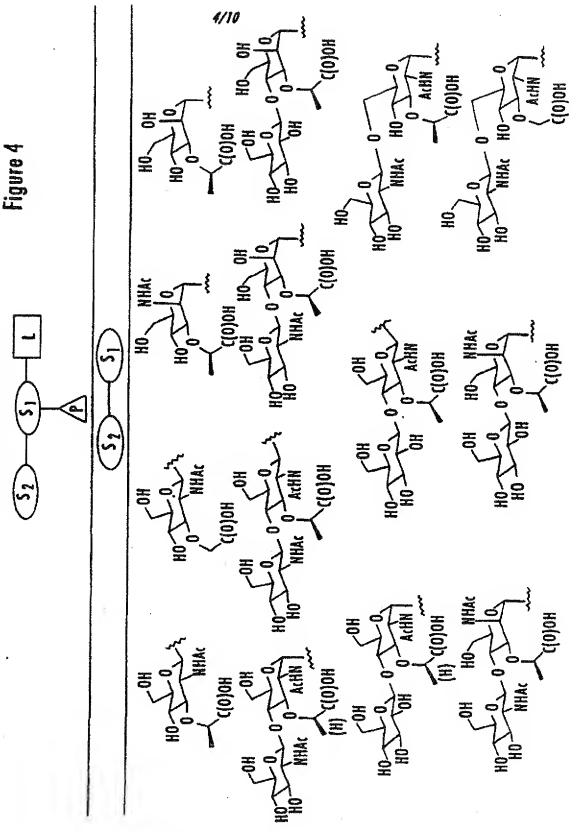


Figure 5

LIBRARY BUILDING BLOCKS

1) L-Ala_D-iso-Gln_L-Lys_D-Ala_D-Ala
2) L-Ala_D-iso-Gln_L-Ar-Lys_D-Ala_D-Ala
3) L-Ala_D-iso-Gln_L-Orn_D-Ala_D-Ala
4) L-Ala_D-iso-Gln_L-Gln_D-Ala_D-Ala
5) L-Ala_D-iso-Gln_L-Lys_Gly_D-Ala
6) L-Ala_4-ABA_L-Lys_D-Ala_D-Ala
7) L-Ala_D-iso-Gln_L-Gln_Gly_D-Ala
8) L-Ala_4-ABA_L-Gln_D-Ala_D-Ala
9) L-Ala_D-iso-Gln_L-Lys_D-Ala
10) L-Ala_D-iso-Gln_L-Lys
11) L-Ala_D-iso-Gln
12) L-Ala
13) L-Ala_L-Ala_L-Lys_D-Ala_D-Ala
14) L-Ala_L-Lys_D-Ala_D-Ala
15) L-Lys_D-Ala_D-Ala
16) Gly_D-iso-Gln_L-Lys_D-Ala_D-Ala
17) Gly_D-iso-Gln_L-Gln_D-Ala_D-Ala
18) L-Ser_D-iso-Gln_L-Lys_D-Ala_D-Ala
19) D-Ala_D-iso-Gln_L-Lys_D-Ala_D-Ala
20) D-Ala_D-iso-Gln_L-Phe_D-Ala_D-Ala
21) L-Gln_D-iso-Gln_L-Lys_D-Ala_D-Ala
22) L-Pro_L-Gln_L-Gln_D-Ala_D-Ala
23) L-Ala_L-Lys_D-Ala

LIBRARY BUILDING BLOCKS
L
S
Sugar — O — P — Lipid
O
Lipid =
R' = Ph, Benzyl, Indole, Alkyl

Figure 5a

Figure 5b

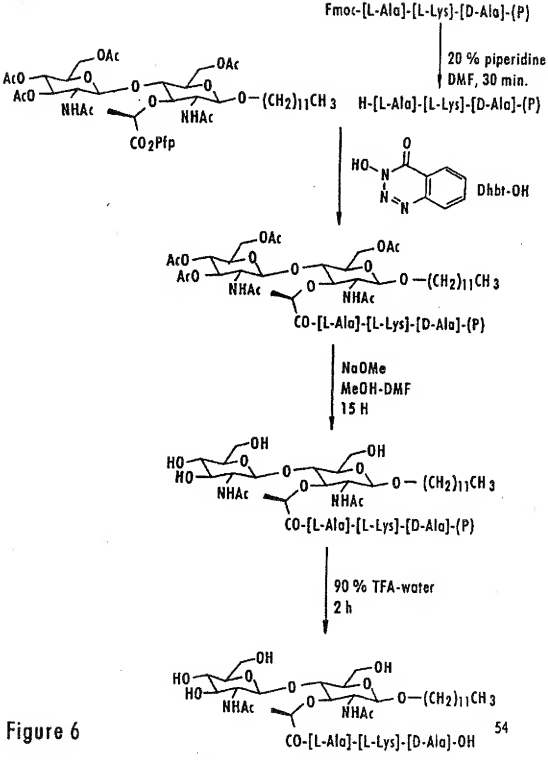

Fmoc-[L-Ala]-[L-Lys]-[D-Ala]-(P)
20 % piperidine
DMF, 30 min.
H-[L-Ala]-[L-Lys]-[D-Ala]-(P)
Dhbt-OH
CO-[L-Ala]-[L-Lys]-[D-Ala]-(P)
NaOMe
MeOH-DMF
15 H
90 % TFA-water
2 h
CO-[L-Ala]-[L-Lys]-[D-Ala]-OH

Figure 6

HIGH THROUGHPUT SCREENING OF GLYCOCONJUGATE LIBRARY
test compound
(1/well)
Ether-permeabilized bacterial
14C-UDP-GlcNAc
UDP-pentapeptide
• Controls and
reference standard
2 hr
37°C
ADD TCA
PRECIPITATE NEWLY FORMED
PEPTIDOGLYCAN
FILTER, COUNT
COMPUTE % INHIBITION OF 14C-INCORPORATION

Figure 7

Fmoc -L-Ala-L-Lys(Boc)-L-Ala-(R)
20 % piperidine-DMF
r.t, 30 min.
H-L-Ala-L-Lys(Boc)-L-Ala-(R)
coupling reagents
(Figure 2)
r.t, 4 h.
(R)= (Cl)-(PS)
(R)= (PEG)-(PS)
(R)= (Cl)-(PS)
4 equiv. NaOMe, MeOH-DMF
r.t, 16 h.
90 % aq. TFA
r.t, 2 h.
90 % aq. TFA
r.t, 2 h.
L-Ala-L-Lys-L-Ala-OH
L-Ala-L-Lys-L-Ala-OH
51
52
8
53

Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04637

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/14;C07H 1/00,15/00
US CL : 530/322; 536/1.11, 16.8, 123.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/322;536/1.11, 16.8,123.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, APS, CA,CAPLUS, MEDLIN, BIOSIS,EMBASE
Search terms: lipoglycopeptides, librar?, combinatorial, inhibitor? ,bacterial, cell wall

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P --- Y,P	CHAN,T.Y. et al. Solid Phase Synthesis of Peptidoglycan Monomers for the Generation of a Combinatorial Library. Tetrahedron Letters 1996, Vol. 37, No. 45, pages 8097-8100, entire document	23-27,29-50 --- 1-22,28,
Y,P	ACS Meeting abstracts, Vol. 211, Part II, Medicinal Chemistry, 24 March 1996, abstract No. 198, CHAN ,T.Y. et al. 'Solid supported Glycopeptide Synthesis for the Construction of a Glycopeptide Combinatorial Library. '	1-50
Y,P	ACS Meeting abstracts, Vol. 211, Part II, Medicinal Chemistry, 24 March 1996, abstract No. 199 ALLANSON, N. et al. 'The Design and Construction of a Combinatorial Glycopeptide Library to Identify Potential Antibacterail Agents.'	1-50

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 MAY 1997	12 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer NEAL A. MUSTO, PH.D
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*